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REGENERATIVE MEDICINE AND THE GOVERNANCE OF STEM CELL INNOVATION

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Contents

Abstract

The aim of this dissertation is to reconstruct analytically and to assess normatively the emerging governance of stem cell clinical translation. I show that the therapeutic promise of stem cell medicine is potentially revolutionary, and that its fulfilment depends on variables that are at the same time scientific and political. The establishment of the governance of stem cell translational research is however taking intricate routes. It is being contested and challenged in many ways by different actors and, most importantly, its development is yet in the making and, hence, uncertain. In this dissertation I show that democracy is called into question by emerging disagreements about the appropriate framing of stem cell innovation. Such disagreements, that are indeed the hallmarks of our pluralistic societies, are relative to the very role of politics with respect to science, citizens' interests, and patients' rights. I therefore suggest that a democratic polity incurs in risks of democratic erosion due to the current political configuration of stem cell translation. I thus articulate some normative proposals as to the political stakes of innovative medicine and I propose technology assessment mechanisms for stakeholders inclusion and public participation to cope with them.

Preface

In the current debate on the political accommodation of widespread moral disagreement, the term 'governance' indicates a shift in the way both academic scholars and policy-makers see the role of politics in highly pluralistic and complex societies. 'Governance', as opposed to 'government', alludes to the open-ended character of the political arrangements that bring divisive issues under democratically accountable political control. This dissertation focuses on the governance of regenerative medicine and, in particular, it aims at reconstructing the emerging governance of stem cell translational research.

The idea of writing a dissertation on the governance of stem cell clinical translation matured slowly throughout the four years of my PhD. Having studied political philosophy as an undergraduate and practical ethics and bioethics as a postgraduate student, my interest in the political conditions of democracy in pluralistic societies extends back to my university period.

The ideas I present in this dissertation grew in the midst of a truly interdisciplinary environment at SEMM (European School of Molecular Medicine). However, in an age of increasing academic specialisation, the statute of interdisciplinary scholars is called into question. On the one hand, many see blurring disciplinary boundaries as a precondition to project oneself into uncharted intellectual territories. On the other hand, however, the interdisciplinary scholar uneasily situates in the academic space if he/she does not bear membership to a specific disciplinary troop. Probably as a consequence of this uncomfortable situation, or probably as a cause to it, interdisciplinary scholarship grew

into a new specialisation itself. In the last few decades, academic journal editors progressively started to ask for interdisciplinary contributions to tackle problems that, arguably, established styles of thought could no longer afford. Among the fields that benefited from this intellectual thread, the study of science and technology more than others took advantage of the convergence between sociology, philosophy, history of science and political science and, more than others, opened up its ranks to collaborations between humanists and scientists. Role exchanges and professional contamination in this field are ever more frequent, and less scandalous, I have to say, than in the past.

As a SEMM PhD student I joined the Science and Technology Studies curriculum of the FOLSATEC (Foundations of Life Sciences and their Ethical Consequences) programme with the idea of specialising on the political management of moral disagreement in the field of the life sciences and biomedical innovation. For almost three fourths of my PhD period I have been actively involved at the bench of molecular oncology laboratories at various research groups at SEMM labs in Milan (IFOM-IEO Campus). This experience was decisive for me to elaborate my ideas on the production and certification of scientific knowledge. As a matter of fact, had I not worked in the lab, in the cell culture facility and in the animal house, had I not attended countless scientific seminars, had I not had the opportunity to meet scientists and clinicians and to discuss with them – my ideas on how scientific statements of fact are generated experimentally and validated communally would have looked quite different.

At SEMM, I could enjoy a climate of open interdisciplinary collaboration, as I have learnt to work at the bench of a molecular biology laboratory, and hence experienced the admixture of pleasure and frustration that this activity entails. However, although versed in molecular biology, and truly enamoured of it, I am not a natural scientist myself. As my work demonstrates, I am after problems of interpretation and normative concerns in the

field of scientific governance and biomedical innovation. During my PhD period I was nonetheless immersed in a remarkably diverse environment, whereby the exchange of ideas between people of different disciplinary affiliations, albeit difficult at times, has been constant, intense and rewarding.

A substantive contribution to the way I see science and its place in society, both intuitively and analytically, came from my colleagues and mentors in the FOLSATEC programme. Over the last four years, our office on campus has been a tremendously stimulating environment of discussion. We shared papers, books and, most importantly, a constant thread of dialogue that, other than providing me with the excellent insights of my colleagues, actually taught me how to think and speak about science, technology and their controversial presence in morally pluralistic democracies. Unfortunately, to my defect, this thesis cannot be but a faint and inadequate rendering of those discussions, but it owes all the good it may contain to the relentless enthusiasm of my fellow PhD students to engage in all-day-long conversations about the politics and ethics of science.

In this period, I had the valuable opportunity to meet colleagues form other institutions as well, and to discuss with them about the topic of this thesis at the Gorino Sullam and Geneva graduate meetings in the philosophy of life science in 2008 and 2010 respectively, and in the 4S Summer School that I attended in Heidelberg in 2008.

The oversight I received from my supervisors was also precious and inspiring. Overall, their constant reminders of following through my own ingenuity and creativity, coupled with moments of seamless circulation of ideas among us, provided me with the necessary encouragement and support.

I presented part of the material contained in this dissertation at academic conferences. In particular, I owe gratitude to the organisers and attendants of two social

science venues, the REMEDiE closing conference in Bilbao in 2011, and the 10th Science & Democracy Network at the Kennedy School of Government – Harvard University later the same year. I have to mention also two scientific conferences where I presented my ideas at a primitive stage and received useful comments from the audience, namely the ISSCR annual meeting held in Barcelona in 2009, and the Reprogramming Cell Fate international workshop held on campus in 2010.

Moreover, I am grateful to the Bio-Objects research platform for financially supporting my 2011 visiting fellowship at King's College, London in the ambit of a EU-sponsored COST Action that brought together a group comprising Prof. Brian Salter and Dr. Alex Faulkner from King's Department of Political Economy, and Giuseppe Testa, MD, MA, PhD and me from SEMM. Joining forces from the two institutions, the group carries on a research project on governance strategies for stem cell translation that naturally connects with and expands on the themes of this thesis.

I am therefore indebted to a number of people for the ideas developed in this dissertation, even though all the errors it may contain are obviously imputable to me, and to me alone.

A further expression of gratitude goes to the members of the FOLSATEC faculty through whose mentorship and support I was able to secure an INSERM EU-funded postdoctoral position at the Faculty of Medicine of the University of Toulouse (Paul Sabatier), in the research group led by Dr. Anne Cambon-Thomsen, starting in January 2012.

Incipit

«Thirty-six fresh or frozen-thawed donated human embryos produced by IVF were cultured to the blastocyst stage in G1.2 and G2.2 medium (25). Fourteen of the 20 blastocysts that developed were selected for ES cell isolation, as described for rhesus monkey ES cells (5). The inner cell masses were isolated by immunosurgery (26), with a rabbit antiserum to BeWO cells, and plated on irradiated (35 grays gamma irradiation) mouse embryonic fibroblasts. Culture medium consisted of 80% Dulbecco's modified Eagle's medium (no pyruvate, high glucose formulation; Gibco-BRL) supplemented with 20% fetal bovine serum (Hyclone), 1 mM glutamine, 0.1 mM β-mercaptoethanol (Sigma), and 1% nonessential amino acid stock (Gibco-BRL).

«After 9 to 15 days, inner cell mass–derived outgrowths were dissociated into clumps either by exposure to Ca^{2+}/Mg^{2+}-free phosphate-buffered saline with 1 mM EDTA (cell line H1), by exposure to dispase (10 mg/ml; Sigma; cell line H7), or by mechanical dissociation with a micropipette (cell lines H9, H13, and H14) and replated on irradiated mouse embryonic fibroblasts in fresh medium. Individual colonies with a uniform undifferentiated morphology were individually selected by micropipette, mechanically dissociated into clumps, and replated.

> «Once established and expanded, cultures were passaged by exposure to type IV collagenase (1 mg/ml; Gibco-BRL) or by selection of individual colonies by micropipette. Clump sizes of about 50 to 100 cells were optimal. Cell lines were initially karyotyped at passages 2 to 7» (Thomson *et al.* 1998, 1147).

The passage above is footnote six of the 1998 paper in which James A. Thomson and his colleagues at the University of Wisconsin described the derivation of embryonic stem cells from early human embryos. The journal *Science* received the manuscript from the research group in early August 1998 and published it a couple of months later as a *Report* in a special issue on neuro-degeneration. It is in a sense surprising that what is now considered one of the seminal papers in the field of stem cell research, the paper that backs the controversial patenting regime of the whole field, and that inspired the formation of an industrial system of promise and hope around stem cell medicine, received no particular emphasis by a journal normally attentive to the wider implications of the science it publishes. In a provoking twist of events however, the *Report* ended up in an issue of the journal that featured a special section on neurodegenerative disorders, today one of the alleged areas of potential expansion of stem cell therapies (see *infra*, Chapter 1). But at the time of publication, stem cells were not the major breakthrough of that week's *Science*.

The stage was for brain degeneration, and *Science*'s cover as well: a diseased brain of an Alzheimer patient, virtually sliced by coronal magnetic resonance scans overlay, rendered pictorially visible the fringes of the brain eroded by the disease in the lapse of one single year. This cover portrays at the same time the vulnerability of what we cherish as the biological site of humanness – the brain – and the relentless effort of science and technology at fighting the disorder and save the patient, and with him, the privileged

symbol of our civilization. This was the image that, with its overload of symbolic layers, got the cover of that issue, not the cell lines Thomson and colleagues established from human blastocysts. After all, the Nineties were the 'decade of the brain', as the US Congress had defined it in staging a major political initiative to support brain research some eight years earlier in 1990 (Jones and Mendell 1999).

This dissertation is about the creation of the political conditions for the fulfilment of the scientific promise that lined up the interests of researchers and the efforts of public regulators in the following decade, the 2000s, and that is now on the verge of attempting to deliver its fruits: curing people with stem cells. Ten years after the derivation of the first human embryonic stem cell line, the expected yield of the field is a paradigmatic shift in our ability to cope with disease, injury, functional degeneration and organ failure. In a future that is yet in the course of being imagined, men and women will resort to regenerative medicine to fight against illness, to preserve the functionality of their organs and to extend the span of their lives (see *infra* chapter 2). But the likelihood of this perspective depends on the success of the current incipient efforts in the field of stem cell clinical research. Such efforts, I will show, are at the same time scientific and political, for biomedical novelty needs be supported, channelled, directed or, in other words, governed politically if it has to fulfil its promises.

Just like the science that it tries to regulate, the governance of stem cell clinical research is sensitive to the accumulation of new scientific knowledge. As a consequence, the array of possible applications of stem cells to the cure of humans solicits the imagination of scientists and physicians in ways that legislators can rarely anticipate. But just like the decade of the brain grew out of a steering political initiative, so does stem cell governance attempt to shape the course of innovation in the fascinating field of regenerative medicine. Moreover, as stem cells make their cautious way towards the

human body through proof-of-concept studies and early-stage clinical trials, new pluripotent entities appear on the stage of science and, seamlessly, become the next hot topic of discussion for public discourses and regulatory design. This propensity of stem cell science to orient sight towards the future turned cellular biochemistry into a site of the imaginary, whereby ideas about therapy interact with newly available manipulative abilities, as well as with emerging legal and political dispensations. Certainly, the journey of imagination that stem cells elicited and that is just starting to align the field toward possible applications, is indeed fraught with controversy. Worries of ethical, legal, political and social nature counterpoint the scientific and technical difficulties that the journey from stem cell research to a new medicine implies. But, albeit in a climate of unsettled public discourses over the wider societal implications of the new regenerative medicine, a remarkably visionary exercise of anticipation lies before us. Thanks to the innovations and transformations introduced by the science of stem cell, what is being deployed is a 'sociotechnical imaginary', that is to say, a "collectively imagined form[…] of social life and social order reflected in the design and fulfilment of […] scientific and/or technological projects"[1](Jasanoff and Kim 2009). As this definition clearly indicates, stem cell innovation is about designing biological entities as much as it is about imagining the users, the practices and the institutions that stem cell technologies will create and require in the future. As it will become clearer in the course of the dissertation, stem cell medicine cannot simply be regarded as introducing a new technique in the arsenal of current Western medicine. The argument I am developing is indeed articulated around

[1] The original definition reads as follows: "collectively imagined forms of social life and social order reflected in the design and fulfillment of *nation-specific* scientific and/or technological projects" (emphasis added). I omitted the reference to the nation-specific dimension that Jasanoff and Kim had included in their formulation, just because it does not necessarily fit with the general initial considerations I am making here. Imagining stem cell medicine, nowadays, is both a global and a nation-specific enterprise. As a matter of fact, the scientific community sees itself and operates as a communitarian entity that cuts across national boundaries. However, the way in which stem cell science is practiced, and the regulatory possibilities of its translation into future therapies very much depend on national legal and political arrangements.

the methodological assumption that stem cell medicine entails much more than this. In particular, I hope I will succeed in clarifying that the challenges awaiting stem cell application to human patients, far from being of a merely technical nature, entail a substantial revision of some current ways of understanding the relationship between humans and the body, as well as a transformation of the regulatory framework governing the circulation of human bodily tissues in our societies.

In this dissertation I will account for the complex dynamics of stem cell regulation in the field of clinical research, tracking the emergence of specific governance models and their contestations, and assessing their ability to cope with remarkable biomedical innovation in a democratically accountable way. Democracy here is called into question by the coexistence of rather irreducible disagreements about the moral value of stem cell research, both at the bench and at the clinical level. Such disagreements, that are indeed the hallmarks of our pluralistic societies, call into question the very role of politics with respect to science, citizens' interests, patients' rights. It is indeed by means of a major rearrangement of democratic practices that regenerative medicine proceeds to its yet uncertain realisation. Even though the fate of early efforts in building regenerative medicine remain uncertain, these very attempts will not leave the face of our democracies unchanged. This dissertation thus attends to an important analytical and normative question: how can and should a polity shape the course of innovation, foster the aims of science and preserve a pluralistic character?

I will therefore, in an orderly fashion, that is to say, under the methodological guidance of the right scholarly tools, try to unravel what is manifest and what is hidden, what reaches the surface of the public debate and what is left unsaid about the way this

particular human activity (i.e. the development of stem cell-based medicine) unrolls into events, discourses and institutions.

Chapter one aims at deploying such scholarly tools thereby making the methodology of this dissertation known to the reader. Chapter two describes the innovation promise of stem cell science with respect to drug screening, regenerative medicine and personalised medicine. Chapter three comprises two parts. In the first part, I will reconstruct the governance models of stem cell research as compared to the established relationship between science and politics in the post-war period. In part two, I will describe how these models have transformed to accommodate the emergence of stem cell *translational* research. In chapter four I will examine the many different routes that stem cell translation is taking and the way the governance model described in chapter three-part two is being contested. Finally, in chapter five, I will assess the democratic quality of the emerging governance of stem cell innovation and propose ways to foster its democratically accountable development.

Chapter 1: Interpreting innovation

In this chapter I will describe the methodological outlook that I will use throughout this dissertation. I will firstly explain what is at stake analytically in trying to provide an interpretation of on-going biomedical innovation (1.1, 1.2). I will then propose to blend a co-productionist account (1.3) with normative insights from deliberative democracy theory (1.5). Moreover, I will justify the possibility and indeed the opportunity to use this hybrid methodology to track the emergence of the governance of stem cell-based regenerative medicine in sections 1.4, 1.6, 1.7, and 1.8.

1.1 Interpreting novelty

A first unavoidable methodological hurdle that my work has to come to terms with is the fact that, to a great extent, what I am talking about here – the transformations that take place around the early steps of stem cell research into the territory of clinical application – lies temporarily ahead of us. The object of my discourse is a particular, and in my opinion paradigmatic, instance of biomedical innovation, one that is not yet entirely with us today and whose chances of being fully realized are, as with most innovative enterprises, deeply obscured by technical and political uncertainty. I am thus speaking of a technology that is in the course of being crafted, both as an object of scientific control and as a politically governable set of medical practices. But that technology is not here

yet. Its delivery has to be located somewhere in the future, provided that it will be delivered at all.

Yet, traces of this possible technological future are already here these days, in the form of texts, inscriptions (Derrida 1976), as political imaginaries and policy narratives (Gottweis 1998, 33-4), and efforts at realizing the possibility of stem cell medicine are potent, scientifically, politically and financially. A trajectory of innovation is starting to coalesce around stem cells, and the early signs of this movement can already be tracked.

All the more, the social science scholar has to develop a methodological toolkit to follow this trajectory, to monitor its development and to deploy its interpretation. Let me thus start by outlining the core tenets of my argument and by justifying the methodological choices that I made in order to elaborate my reasoning about it.

The argument that I am developing around this early trajectory is that stem cell translation, albeit being at an early and uncertain state, is reaching an unprecedented degree of social and political relevance, one that at least parallels the scientific import of its findings, and that dictates a thorough normative reflection on the actual state of our democracies. The reason for calling democracy into question with respect to biomedical innovation is grounded in many years of scholarship in STS that, as the field started to look at policymaking as a major site of scientific controversy, investigated the role of science in disputes of political representation and decisional accountability. In particular, biotechnology provided a wealth of empirical material to comparative studies on the various regimes of governability (Gottweis 1998, 31) that arose around emerging scientific novelties. Those regimes were shown to rely on linguistic resources to form and sustain themselves. In Gottweis' words,

> «[n]arrative and discourse underscore the idea that the boundaries of politics, science, and technology are always drawn within the larger semiotic context of the various stories that give a society its identity and hold it together» (Gottweis 1998, 31).

Drawing on post-structuralist discourse analysis, this perspective emphasises the shifting relationship between power and language in social phenomena. According to a post-structuralist scholar, the object of social analysis is "the continuously fluctuating ways in which speakers, within any discursive context, are variously positioned as powerful or powerless by *competing* social and institutional discourses" (Baxter 2002). This outlook, as it will become clearer in the course of this dissertation, fits conveniently to describe the emerging governance of stem cell clinical research. It is therefore discourses and power-granting institutional relationships between regulatory agencies, legislators, scientists, clinicians and patients that constitute the object of my analysis.

From this perspective, policymaking looses the connotation of a socially separate *quasi*-technical administrative activity, to be better understood "as an attempt to manage a field of discursivity, the intermediation between policy narrative, […] and discursive context" (Gottweis 1998, 37). The creation of political stability around science is thus to be seen as depending on linguistic resources other than on the availability of administrative positions. Controversies over the use of biotechnology in the last three decades have demonstrated that such a space of discourse and power can only be stabilized when, "in a continuous process of debate and reciprocal persuasion" (Majone 1989, 1) that characterizes any democratic political system, one narrative becomes, at least temporarily, dominant over the others.

Stem cell research, with the wide, open-ended and un-stabilized array of conflicting narratives that arise around its controversial use, is but a late instance of such discursive circulations; one that is worth analyzing however, for it exemplifies the still on-going process of modifications that biotechnology is realizing on society at large. Stem cells should thus be seen as an innovation that contains the germs of a wider societal transformation whose direction this dissertation aims at critically appraising. As a matter of fact, it should hardly be surprising that stem cell research acts as a site of both biomedical and political change: as Sheila Jasanoff put it, "[t]he dynamics of political power, like those of culture, seem impossible to tease apart from the broad currents of scientific and technological change" (Jasanoff 2004, 14).

A major overall premise of this dissertation is exactly the realisation that, as a biotechnology grows, the relationship between science and the polity changes profoundly. Stem cell innovation will therefore work as a privileged vantage point to analyse one of the latest instantiations of this transformative trajectory.

1.2 A hybrid methodological toolkit

From a methodological point of view I will thus need two things. First, in order to appreciate the societal import of stem cell innovation, I will need a theoretical framework that captures the symmetric construction of knowledge, technical skills and governance tools. Second, in order to assess the impact of such structured innovation trajectory on the trim of democracy, I need a political theory indicating how change is discursively handled in a democratic polity, especially with respect to the kind of conflicts and disagreements that are typically elicited by the advance of the life sciences. Furthermore, it would be desirable that these two elements of my toolkit be themselves

methodologically related in some theoretically meaningful sense. Therefore, I will justify my choices below not only individually, but also as a bundle. As such, this hybrid bundle will lay down the methodological foundations of what I propose to call a political philosophy of biotechnological innovation.

Let us thus begin with the first component of the bundle. As I already anticipated (see *supra*), stem cell translational research is a complex area of innovation. Therefore, in investigating this contemporary area of biomedicine, I need a framework that, while fully acknowledging this complexity, allows me to make sense of it. To this aim, I will adopt the theoretical viewpoint of the co-productionist framework. The latter is supposed to allow me to look at the uncertain emergence of a new technology as constructing, at the same time, the epistemic, technical and regulatory conditions of innovation.

As it may already seem apparent to the academic reader, I am, from the very onset of my work, using the word 'innovation' to encompass the technological yield of stem cell research as well as the societal import that the presence and circulation of stem-cell objects and clinical practices imply. The fundamental thread of this thesis is therefore that the trajectory of biotechnological innovation, realized by early efforts at translating stem cell knowledge and practices from the lab to the clinic, cannot be observed assuming a pre-given separation between the product of innovation and the societal arrangements that allow such product to be crafted, circulated, commercialized, used to heal human patients, and debated within the polity. I thus underwrite to the co-productionist idiom that has recently emerged in the field of science and technology studies (Jasanoff 2004, chapters: 1, 2, 13, 14), as it proved better equipped than other more traditional accounts to make sense of the messy relationship that technology and power entertain in contemporary democracies. More specifically, neoclassical accounts of technological innovation, used to see knowledge production as distinct from the social

activity of firms and regulators that use that knowledge or try to steer its production (Nelson 1959; Arrow 1962). The production of knowledge, and the ordering of society with respect to innovation thus fell on separate sides of an imagined divide between science and society, facts and norms. In those accounts, the only point of engagement or interface between creators of knowledge and creators of social ordering in those accounts, were research and development (R&D) budget allocation decisions. But in the age of biotechnology, and in the face of the profound cultural controversies that inspire debates around biomedical innovation, those kinds of approaches and their vocabulary do not offer satisfying insights into what is really at stake with the advancement of the life sciences.

1.3 A co-productionist idiom

Co-production is a methodological framework developed in STS. It especially owes to the scholarship of Sheila Jasanoff (Jasanoff 2004), and to her effort at providing the growing field of STS with solid methodological bases. The prolific academic activity of Jasanoff and other prominent scholars in STS have given rise to a huge amount of empirical and theoretical analyses of technological phenomena. The field applied the co-productionist agenda especially to policy decision-making on scientifically sensible issues, thereby producing a wealth of academic literature on problems such as scientific advice (Jasanoff 1994; Bal, Bijker, and Hendriks 2004; Bijker, Bal, and Hendriks 2009) and the role of experts in policy choice (Fischer 1990; Weingart 1999; Jasanoff 2003a; Nowotny 2003; Maasen and Weingart 2005; Collins and Evans 2007; Bijker, Bal, and Hendriks 2009; Fischer 2009). The main tenet of this stream of analysis is that “it is through systematic engagement with the natural world and the manufactured, physical environment that modern polities define and refine the meanings of citizenship and civic responsibility, the

solidarities of nationhood and interest groups, the boundaries of the public and the private, the possibilities of freedom and the necessity of control" (Jasanoff 2004, 14). The theme of boundary construction and deconstruction, appearing towards the end of the quote, is indeed among the main tools in the hand of co-production oriented STS scholars. Originally elaborated by Gieryn to account for the demarcation of science from non-science (Gieryn 1983; Gieryn 1995), the idea of 'boundary work' aims at analysing "the attribution of selected characteristics to institutions […] for the purpose of constructing a social boundary that distinguishes" them from others (Gieryn 1983, 782). It is just about the case of stressing the linguistic nature of such attribution games: it is through communicable statements, visible practices, and public institutional arrangements that social actors build up and negotiate the boundaries of their agency, and thus exercise power onto other actors, or create the conditions for doing it. Those negotiations, like any other form of inscription, leave traces that the analyst can follow or try to reconstruct, when they, due to cunning exercises of black-boxing (Latour 1987), are too faint to be clearly seen. Therefore, it is on the background of a social constructivist approach, broadly conceived, that the idea of boundary work contests conceptual and social dicotomies – such as facts/values, science/non-science, expert/non-expert, basic science/applied research, natural/artifactual, tool/use, technology/ governance – that typically appear in discourses about science and its place in society. STS has shown the heuristic poverty of assuming that those demarcations simply exist, like immutable metaphysical entities, thus obscuring the rumbling social activities aimed at filling those twosomes with different meanings at different occasions. This interpretative paradigm seems particularly fit to describe the kind of simultaneous and mutual production of knowledge and social order that happens to take place in biotechnology, where meaning, values and power have no less a fundamental creative potential than scientific discovery

and medical application. To use Jasanoff's words, "several decades of research in science and technology studies have done much to illuminate how orderings of nature and society reinforce each other, creating conditions of stability as well as change, and consolidating as well as diversifying the forms of social life" (Jasanoff 2004, 17). It thus seems tempting to adopt the co-productionist idiom to describe the precarious and uncertain technological trajectory like the coming into being of stem cell medicine.

The co-productionist account of scientific and technological phenomena brought in the hands of social scientists an unprecedented explanatory power: co-productionist analyses are able to detect power games and stabilization dynamics directly into the formation of scientific knowledge and the production of technological objects, and to account for the diversification of the sites where the latter activities are carried on. In this respect, particular attention is paid to the formation of discourses within political institutions like governmental agencies, parliaments and courts that, while deploying their regulatory dispensations, at the same time produce techno-scientific narratives in the form of more or less outspoken visions on the future social arrangement that will surround an emerging technology. In the last decades, and under the increasing pressure of biotechnology, the latter sites gained prominence as forums of public debate over the use and limits of innovation. In this sense, the co-productionist agenda encompasses more that an explanatory function to unravel the social negotiations that constitute a space of discussion and public decision. Major technological disasters, like Bhopal, or Three Mile Island, disputes about the use of pesticides or genetically modified food, as well as judicial disputations on the use of expert testimony or the admissibility of patent protection on gene sequences – such issues, and similar episodes of scientifically driven public contentions, received sustained attention by STS scholars in recent years. Given the nature of those phenomena that STS takes as the object of its analyses – showing

how politics and knowledge, norms and facts, entertain a mutually productive dynamics – the field legitimately aimed at having a normative bite. In the next section I will analyse the content and, in my opinion, the limits of co-productionist normative concerns.

1.4 Concerns of normativity

The realization that science, just like any other human activity, is amenable to a sociological analysis that deconstructs its internal norms as socially determined, led the positivistic assumptions of Mertonian exceptionalism (Bimber and Guston 1995) to a progressive decline starting from the Sixties. In the span of almost four decades, social constructivist sociology of scientific knowledge (SSK) have convincingly argued that "it is necessary to draw on 'extra-scientific factors' to bring about closure of scientific and technical debates – scientific method, experiments, observation, and theories are not enough" (Collins and Evans 2002, 239). This view resulted in a huge literature on the problem of scientific expertise and political decision-making. In a remarkable display of intellectual contagion, those ideas quickly attracted support within the public sphere of Western societies in the Seventies, years of unfavourable social attitudes towards any kind of authority – political, philosophical and epistemic as well. However, two major normative contributions of the field to the debate on scientific expertise in public matters are worth recalling here. First, the realization, against technological determinism, that scientific development by no means follows a deterministically established and immutable trajectory: being the production of knowledge and technology a historical phenomenon, it is feasible to conceive of alternatives within the possible routes of development of a given technological apparatus, and it is possible to act, politically, to change the course of this development. In the words of Andy Stirling,

> «the form and orientation taken by science and technology are no longer seen as inevitable, unitary, and awaiting discovery in Nature[;] instead they are increasingly recognized to be open to individual creativity, collective ingenuity, economic priorities, cultural values, institutional interests, stakeholder negotiation, and the exercise of power» (Stirling 2008, 263).

Second, and as a logical consequence of the latter critical attitude, the normative concerns of the field took the form of a plea for resolving "the Problem of Legitimacy [i.e. why should we trust scientists if they no longer appear to have special access to the truth?] by showing that the basis of technical decision-making can and should be widened beyond the core of certified experts" (Collins and Evans 2002, 237).

This call for the democratization of expertise obviously took many forms (see Liberatore and Funtowicz 2003, whole issue), and also gave rise to some theoretical and practical proposals (Funtowicz and Ravetz 1993; Collins and Evans 2002; Jasanoff 2003b; Timmermans and Berg 2003; Hoppe and Wesselink 2011), mostly having to do with coping with the 'problem of extension', that is to say, establishing how far participation in technical decision-making should extend (Collins and Evans 2002, 237). Critical thinking, democratization, widened participation, re-negotiation of the boundaries of scientific expertise to include unheard voices into decisional mechanisms – these rapidly became the most pressing topics of a conceptually and empirically rigorous debate about science and society.

On this front however, several commentators noticed the difficulty of science studies, including STS and co-production, in elaborating a coherent normative discourse or, more simply, in providing ethical and political guidance for the reasonable stabilization of techno-scientific controversies (Winner 1993; Collins and Evans 2002). Winner has

argued for instance that in spite of an almost obsessive concern for deconstructing and reconstructing the conditions of emergence of knowledge and technology, the field has generally lacked a full-fledged interest for debating about the consequences of technological development (Winner 1993). This allegedly resulted in – and probably was caused by – a rather apparent paucity of methodological tools to articulate a robust normative response to the political issues that science and technology scholars so wittingly have isolated.

In broad terms, I agree with those critics and with their methodological preoccupations. It would however be unfair to the field of STS, to deny that defined streams of normative and political propositions flow under the surface of most co-productionist accounts of science and technology. And if those ideas rarely, if ever, reached the status of cogent moral or political theory, it is not imputable to the inadequacy of the co-productionist framework, nor to a certain idolatry for explanatory research and methodological purity. Rather, this outcome is the result of a certain post-modern diffidence towards grand philosophical '*recits*' (Lyotard 1984) that, claiming a privileged access to universal moral truth, see themselves as severed from the historical flow of social phenomena and immune to the power relations that instead, according to STS, should be the focus of analytical inquiry. In particular, along these lines, some strands of STS have developed a critical stance towards bioethics and political theories. They are accused of relying on fictitious assumptions about how ethical controversies are dealt with in society (Evans 2002). In particular, STS scholars have criticized the idea of the individual agent of the liberal tradition as embodying unreal attributes of rationality and disinterestedness that are never found to be really at work in the kind of controversy analysis that STS performs. Besides these epistemological concerns, the language of liberal bioethics is thought to be functional to the advancement of scientific interests, and

rather exclusive of the kind of culturally situated stakes that other actors might have with respect to biotechnological innovation, and that deserve to be included in the democratic decision-making process. Therefore, liberal bioethics would inevitably be linked to the technocratic aspirations of scientists and technologist, thus enacting a distinctive anti-democratic trait. Especially troublesome to STS scholars are power imbalances that characterize policy-making processes focused on the governance of science. One can thus conclude that STS, far from being normatively inert, shed light on problems of political representation in decisional contexts about science, albeit, consciously, in an under-theorized fashion. In my view, such normative drive has the merit of bringing unjustified power relations to the surface of discourses that tend to overlook power distribution issues in public policy, thus calling for a more democratic negotiation of the inclusion criteria in decisional settings (Funtowicz and Ravetz 1993).

However, I see three problems with such normative tendencies. First of all, I think scientific credibility is not lost upon sociological deconstruction. As I already said above, a STS outlook on socio-scientific controversies is founded on a social constructivist vision of science. If this has the merit of overcoming dicotomies between science and other human activities, thus rendering a more realistic picture of how epistemic practices lead to the articulation of scientific facts, this outlook should not be pushed too far. It is certainly true that the credibility of science as a dispensator of positive truths about nature has a strong socially constructed component: in this respect science is amenable to deconstructive social analysis just like any other human activity. It is however unnecessary to stretch this consideration to the limit of saying that all socially constructed activities are epistemically equivalent. Without entering a philosophical debate that has been occupying specialists for centuries, we can say that science, albeit uncertain and controvertible, still has to offer the pragmatically most reliable accounts of

natural phenomena that human civilization has ever produced – precisely for its accommodation of uncertainties and regular scrutiny of certainties. This is not to say however, that those accounts have nothing to do with the aspirations, interests and visions of the world of people inside and outside the scientific community. In other words, science is not a pre-social activity having to do with pure nature and yielding pure statements of fact (Nagel 1989). To the latter point, I think STS scholarship has provided all the empirical and theoretical evidence to believe that, indeed, scientific statements are sensitive to the social *milieu* that produces them and have consequences, cultural and institutional, that amply surpass the boundaries of a purportedly independent scientific community. But science is nonetheless the most reliable source of knowledge about biological and physical phenomena, and the burden of unmasking scientific statements as sheer social constructions that offer no more reasonable motivation to be believed than other, clearly non-scientific kinds of knowledge, is on the shoulders of extremist social constructivists. To the extent that social constructivism, on the basis of scientific controversies and technical failures of the past, embraces an *a priori* anti-scientific position that systematically disregards science as a credible partner in policy-making, it is a normatively unhelpful standpoint. Weaker versions of this attitude are indeed reflected in the methodological commitment to be symmetrical or, as it is sometimes otherwise said, agnostic with respect to the truth functionality of the scientific claims that the analysis encounters (Latour and Woolgar 1979). It the words of Winner,

> «as regards to the analysis of scientific knowledge, the epistemological program of relativism in the sociology of science remains neutral as regards judgments about whether or not the proclaimed discoveries or theories of scientists are true or not. Extrapolating to technology, social constructivists choose to remain agnostic as regards

the ultimate good or ill attached to particular technical accomplishments» (Winner 1993, 372).

Therefore, to sum up this first consideration, the epistemic reliability of science is not debunked by its being amenable to sociological deconstruction.

The second problem I see in the engagement of STS with normative discourses about science and technology is far more specific and relative to political considerations. The political focus of the discipline, as it is evident from the scholarly work of its representatives in the field of expert decision-making, is on problems of representation rather than on problems of political legitimacy. Collins and Evans, although I very much agree with the overall aims of their famous 2002 paper, are wrong in characterizing STS concerns for the democratization of expertise as having to do with *legitimation*. As it results from the ever-mounting body of literature on widening participation in decisional settings about science, the normative drive of this strand of scholarship has to do with having more voices heard than technocratic arrangements would allow. The focus is thus not on the justifications that end up backing a given decision (i.e. legitimation proper), but on the distribution of participants across the boundary, or as one should probably say, the gradient of expertise that severs scientists and lay citizens. The emphasis is thus on how to provide all relevant stakeholders a chance to influence the decisional outcome, irrespective of the actual content of the final decision. This procedural concern is directed towards re-balancing the distribution of power and the relations of authority that hold at any important political junction. The aim is therefore that of taking political *representation* seriously, not that of interrogating a particular decisional situation to assess, in a purportedly disinterested way, whether sufficiently sound reasons subsist to rationally *justify* the policy at stake. It is thus linguistically unwarranted to dub this concern as 'The Problem of Legitimation', as Collins and Evans do. In other words, STS has

been concerned mainly with what happens at the decisional pole of a controversy about science and technology. This is consistent with STS Foucauldian interest with power relations. But, I would argue, this attitude misses the actual prominence of legitimating discourses in "stabilizing the political space" (Gottweis 1998, 37). The free circulation of legitimizing discourses in the public sphere relies on resources that certainly include fair representation, but are by no means restrained to it. In every polity, there exist a multitude of publicly relevant decisions that are legitimately captured by delegated specialists having not even the slightest intention to be representative of the full spectrum of potential opinions that may circulate in the public space. This is not to say that the decisional authority of even those kinds of specialists cannot or should not be questioned. On the contrary, it is advisable that a polity retains the political and discursive resources to publicly engage in anti-authoritative initiatives, be they addressed at enlarging the decisional bases, thereby advancing a plea for increased representativeness, or at directly questioning the very content of a given decision. Legitimation, as I will illustrate below, depends much more on the possibility of alternative discourses to be continuously articulated, circulated throughout society and directed against dominating narratives, rather than merely on balancing forces at decisional sites. Although a fair distribution of power at the moment of policy-making is functional to an effective circulation of discourses, it does not exhaust the politically legitimizing role of argumentative discussion within a polity – the reason being that decisions arrived at by a more representative panel, *per se*, cannot lay claim to a privileged access to incontestable political wisdom. Therefore, it may be useful that the focus of analyses that, like mine, are interested in following both the emergence and the potential political consequences of a global biomedical technology like stem cells, has to be on how a polity *deliberates* rather than decide about a certain issue (see *infra* 1.5).

In order to stress the importance of deliberation, as contrasted but not opposed to decision making, it is thus desirable to look at philosophical accounts of politics that go under the name of deliberative democracy theories. Before introducing the main tenets of a deliberative conception of politics, let me briefly enunciate the third reason behind my scepticism towards the normative intentions of the STS framework. In the face of its impressive explanatory power, STS has evolved a good degree of self-awareness about its methodological consistency. Furthermore, it has programmatically refrained from acquiring the status of a full-blown *theory* of scientific and technological phenomena, both because of its above-mentioned diffidence towards philosophical discourses and for an apparent lack of necessity to adopt a crystallized vision that would have greatly limited the richness of approaches that the discipline continues to harbour. STS has thus been reluctant to look into the portfolio of available political theories a bit more carefully to find possible systematic integrations and theoretical partnerships. In this respect, I think it is high time since the field shows its potential at informing the normative discourse a bit more consistently, or at least at integrating the public debate about science and technology with the specific insights of co-production.

We have therefore come to a point where a possibility starts to become visible: that of complementing the co-productionist agenda (along the critiques just developed) *via* the tools of a theoretical account of how public disputes about the production and use of knowledge could be resolved in a democratic polity. In the next section I will introduce the basics of a deliberative theory of democracy – one of the latest and more debated realizations in political philosophy – as a framework that can direct STS towards a methodologically more controlled exploration into normative territories, without contradicting the insightful premises of the co-productionist agenda. I will show that the deliberative democrat can indeed appropriate STS main normative threads, and

viceversa, that the STS scholar can see its epistemic and normative commitments at work within those of deliberative theories of democracies. In particular, the two accounts match together elegantly, as both emphasise: 1) the critical role of discursive practices at deconstructing authority and thinking of possible alternatives to current political arrangements around science; 2) the necessity for inclusion and participation of all stakeholders in the debate on science policy; 3) the need for the stabilization of public conflicts about science through innovative institutional design rather that authoritative closure. Finally, to this last point, both accounts have tools to say that at deliberative sites, discursive dominance is and should remain revisable, and reliant on persuasion rather that on a politically hegemonic aspiration to moral universality (Hamlett 2003).

1.5 Deliberative theory

An analysis that aims at making sense of the policy space that emerges around the rise of a politically controversial technology like stem cells, cannot do without an outlook of the nature of the state. This is so for a basic methodological reason. In order to explore that space and make it subject to a normative discourse, one needs to be able to look at it in a way that captures the ways in which politics plays out both as a partner and regulator of scientific and technological development. To this end, I decided to adopt the co-productionist framework. But in order for the analysis to make sense of how those issues impact on the democratic estate, it has to rely on a theory of the state of some sort. In this regard, what is emerging within the last decades of scholarship on political theory, is a growing consensus on the adequacy of looking at the democratic state as a community of discussants. Political scientist Giandomenico Majone has highlighted the pervasiveness of a discursive character in democratic polities with great clarity:

> «Discussion goes on in any organization, private or public, and in any political system, even a dictatorship; but it is so much at the heart of democratic politics and policy that democracy has been called a system of government by discussion. Political parties, the electorate, the legislature, the executive, the courts, the media, interest groups, and independent experts all engage in a continuous process of debate and reciprocal persuasion» (Majone 1989, 1).

Thus, according to Majone, and a number of adherents to the deliberative paradigm as well, discussion occurs at many sites in a polity, not only in the highest spheres of institutionalized political bodies. What can immediately be observed is that political decision-making mainly occurs in constitutionally specified sites, or in powerful private organizations that, due to the nature of their activities or to the greatness of their interests, are able to make decisions that not only bear on a number of people inside and outside of them, but ultimately become of public relevance for all. For this reason, as I said above, the problem of fair representation of interests and points of view at decisional sites has been occupying the debate in a rather dominant fashion. Deliberative theories however, shift the focus of theoretical attention from the pole of *decision* to that of *discussion*. This is not meant to disregard the obvious importance of decisional activities as to the consequences of policy on the well-being of the political community and of its individual members. Rather, deliberative theories draw on the realization that arguments, views, and interests, can assume a linguistic articulation and travel within the polity, thereby eventually even reaching decisional locations and informing their proceedings. To this point Gutmann and Thompson have proposed the notion of 'middle democracy' to indicate that the forums of deliberation extend beyond "legislative sessions, court proceedings, and administrative hearings" to include "meetings of grass roots organizations, professional associations, shareholders meetings, and citizen's

committees in hospitals and other similar institutions" (Gutmann and Thompson 1996, 13).

The idea of middle democracy is but a realization of the necessity to enlarge the scope of the political sight into previously un-thematized spaces. Jürgen Habermas, with his thorough analyses of the so-called public sphere, has probably been the most prolific among the philosophers who articulated this shift in political focus from institutionalized decisional sites to less-structured, though not amorphous, spaces of discussion (Habermas, 1989).

These ideas started to develop, at least to some extent, in response to dominating academic debates in the philosophy of politics of the Seventies. In those times, political philosophers where mainly concerned with issues of social justice. They started from the realization that classic liberal rights and freedom are rather empty concept in the presence of strong social inequalities. To tackle this problem, philosophers like Rawls, Nozick and Walzer elaborated radically contrasting theories of justice (Rawls 1971; Nozick 1974). According to early deliberative theorists however, those accounts imported from the classical liberal paradigm that they were trying to criticize a distinctively philosophical aspiration to universalist solutions (Manin 1987). In other words, Rawls' philosophy, for instance, while eventually tackling the problem of how to fairly distribute resources throughout society, did so "to demonstrate the rational and universally acceptable character of a theory of justice that bases the actions of the state on broader functions than those of the minimal state" (Manin 1987, 339). This attitude also reflected a long held tradition in classic political philosophy debating political justification in terms of unanimity rather than majority rule (Rousseau 1970). According to Manin, and other deliberative democrats as well, these theoretical traditions rely on unnecessary and unjustified assumptions regarding the nature of human political agency. In particular,

deliberative democrats contest that the idea of political legitimation requires unanimity, that political choices happen without deliberation, and that the will of individuals is predetermined and fixed at the moment of political decision (Manin 1987, 347). These features can be seen to be operational in both classic accounts of legitimate political choice, and in modern theories of justice – of whatever orientation. However, in real world situations, it is never the case that individuals have all the information to make an insulated decision according to their pre-determined will. In other words, "there is […] no reason to suppose that individuals have from the first a complete set of preferences" (Manin 1987, 349). In debates about biotechnology for example, this assumption often plays a politically destabilizing function, as it attaches to either sides of public controversies the incapacity to reach reasoned convergence towards the opponent's assessment – thus reducing the debate to sheer bargaining of contrasting and irreducible interests.

In the light of the realization that, in a deliberative exercise participants' preferences, opinions and objectives can well be modified, deliberative democrats invite a renewed reflection on the actual sources of political legitimation. As soon as the discursive character of democracy, as well as the opinion- and will-formation potential of deliberative engagement are taken at face value, it becomes evident that deliberative democratic theories see the source of political legitimacy not to coincide with the predetermined will of individuals, but rather to come from the multifarious process of will-formation through deliberative exchange.

By stressing the importance of the discursive negotiations that precede and accompany policy-making activities of statutory bodies, deliberative theorists successfully showed the reliance of democratic institutions on a democratic culture, one in which citizens actively participate in a continuous self-reflective exercise of discussion on issues

of public interest. In large democratic polities, not everybody can decide, and representation, as fair as it may be, cannot include every dissenting voice. According to the deliberative outlook of politics, however, these rather fundamental unbalances in representation, albeit impossible to resolve even trough democratic constitutional arrangements, can be valuably mitigated in their erosive effects through widespread deliberative engagement. Following a schematic articulation, Habermas claimed that "[i]nformal public opinion-formation generates "influence"; influence is transformed into "communicative power" through the channels of political elections; and communicative power is again transformed into "administrative power" through legislation" (Habermas 1994, 28).

Such conception of the transformation of public opinion into administrative power through linguistic mediation reflects what I had indicated above as the necessity to deflate the analytical focus on representation and to give legitimation issues more prominence in our analysis. As Habermas also recognizes, emphasising the discursive circulations that take place within the public sphere, "has implications for how one understands legitimation and popular sovereignty" (Habermas 1994, 28). The idea of the public sphere, as originally advanced by Habermas (Habermas 1989) "designates a theatre in modern societies in which political participation is enacted through the medium of talk [and] in which citizens deliberate about their common affairs, hence an arena of discursive interaction" (Fraser 1990, 57). As such, the public sphere "is conceptually distinct from the state; it is a site for the production and circulation of discourses that can in principle be critical of the state" (*ibidem*). The advantage of a discourse theory-based idea of politics consists in favouring the realization that "the procedures and communicative presuppositions of democratic opinion- and will-formation function as the most important sources of the discursive rationalization of the

decisions of an administration" (*ibidem*). The latter should be conceived as "a subsystem specialized for collectively binding decisions, whereas the communicative structure of the public sphere comprise a far-flung network of sensors that in the first place react to the pressure of society-wide problematics and stimulate influential opinions. In this way, "public opinion that is worked up via democratic procedures into communicative power cannot "rule" of itself, but it can only point the use of administrative power in specific directions" (Habermas 1994, 29). This instructive function, however feeble it may be with respect to the self-sustaining systemic authority of legislative and administrative power, is the ultimate source of legitimation for any publicly binding policy. From the standpoint of legitimation, the first and foremost role of the public sphere, so conceived, is that of monitoring the state authority through informed and critical discourse (Habermas 1989). In this respect, the *bourgeois* public spheres that formed in the XVIII century, and that Habermas analysed, may represent a blueprint of rational opinion-formation gatherings "emancipated from the bonds of economic [and political] dependence".

In order to account for the value of discussion in associative life, theorists often adopt classic definitions of deliberation and discursive exchange. Accordingly, some characterize a discussion-based mode of politics with reference to the Aristotelian notions of 'dialectic' and '*prohairesis'*. These concepts, however, are both philologically contested and philosophically aporetic within the texts of Aristotle (Chamberlain 1984; Hamlyn 1990), and their meaning should thus not be taken to encompass a full-blown endorsement of Aristotle's ideas about human agency, ethics and politics. Nevertheless, it is useful to briefly discuss their original meaning to illuminate their function in today's political debate.

The notion of *prohairesis* (deliberate choice) is the Aristotelian analogue of what democratic theorists today refer to as deliberation[2]. As I just said the real meaning of this notion in the writings of Aristotle has been a matter of long exegetical debates. To our aims here, it suffices to remind that *prohairesis* might be taken to mean "desire involving deliberation" (*orexis bouletikê*), that is to say a rational way of choosing what a correct desire establishes as an end (Arisotle, 2009, EN 1139a23). Discussing the notion of 'correctness' (*orthotes*) of desire would lead us into the intricacies and fallacies of Aristotle's moral thought. The notion of desire, nevertheless, can be said to have a crucial role in this account of deliberate choice: the desiderative component of the soul establishes an end to action but, contrary to schematic interpretations of these notions, this end is not set once and for good. Choice, other than being simply the juxtaposition of goal-setting desires and mean-finding reasons, is also about changing desires according to reason. In other words, deliberate choice "is the process of consciously deciding to form and of forming a new desire" (Chamberlain 1984, 153). How much this interpretation is grounded in the writings of Aristotle is up to others to dispute, but certainly it corresponds to what philosophers these days take to be a model of deliberative engagement: one whereby participants, rather than negotiating unchangeable interests, discuss the stakes of public issues in an open-minded fashion. That is why theorists like Habermas emphasise the public space of deliberation as a site for opinion- and will-formation, rather than the location of actual decisions. It will become clear later in the dissertation that science should look at the public sphere as the most important space of cultural agency in view of the stabilization of the controversy that it tends to generate.

[2] In the English speaking world the word '*prohairesis'* has not been translated with 'deliberation', so it might be misleading to attribute this particular Aristotelian ascendancy to deliberative theories. The Aristotelian term that most translators have rendered as 'deliberation' is '*boulêsis',* which means calculation of the appropriate means to pre-given ends (NE III, 4 and 5). However it is '*prohairesis*', in the sense specified above (see main text), that deliberative theorists have in mind when they speak of deliberation with reference to Aristotle.

The other classic reference notion for deliberative accounts of politics is 'dialectic'. Dialectic is a form of discursive proceeding that is distinct from rational demonstration. Whereas the latter relies on necessarily true premises, and allows to deductively come from them to logically binding conclusions, (through the mediation of middle terms in demonstrative syllogisms), the dialectic process starts with premises that, while enjoying a lesser degree of certainty, are accepted "by everyone or by the majority or by the wise" (Aristotle 1997, Topics I.1, 100b21-3). Despite this difference, both the syllogistic method of science and the dialectic are deductively sound operations. A discussion of the relationships between dialectic and demonstration goes beyond the scope of this dissertation. What is relevant to our present investigation, however, is the fact that dialectic points the attention of contemporary political philosophers to focus on the conditions for the acceptance of a given position as offered in publicly staged deliberations. Such conditions, like in Aristotle, have not much to do with the necessary truth that a given statement can demonstratively exhibit during deliberation. Rather, it has to do with how persuasion builds on less than certain discursive resources that might nevertheless be conducive to reasoned agreement. Therefore, appealing to this ancient notion as informing deliberative exchanges, deliberative policy analysts achieve a double gain: on the one hand, very much in the style of co-production, they deconstruct the relationship between truth and power, therefore also undermining the technocratic image of science as 'speaking truth to power'; on the other hand, moreover, they retain a view of public dialogue as a reasoned exercise, one that, when it informs policy making, can provide some acceptable criteria of justification to publicly binding decisions about matters of general concern. In this sense, deliberation is both a mean of contestation of established authorities, be they epistemic, political or economic, and a means of

stabilization of a public space that, especially in the case of biotechnology, may well be perturbed by the turmoil of moral disagreement.

This is not to deny, however, that powerful agents can indeed end up capturing the game of persuasive exchange of reasons in a deliberative context and steer it to their own private advantage. Very much in line with the co-productionist ideas, deliberative democracy and its associated conceptions of the public sphere have indeed recognized the unavoidable tendency of persuasion to occur outside of an idealized and disinterested trafficking of deliberative reasons (Habermas 1989, ch V, VI). Furthermore, under the influence of Marxist and feminist thought, scholars in this strand of political philosophy have remarked the hegemonic potential of a public sphere that, albeit engaged in deliberation, restrains the spectrum of the admitted discursive practices to those that are functional to specific cultural and material interests (Landes 1988; Fraser 1990; Benhabib 1992; Ryan 1992; Eley 1994). Deliberative democrats however, have elaborated arguments to reply to those critiques. In particular, the formation of deliberative cirlces has been conceived as an institutionally informal activity, one that can happen spontaneusly outside state-controlled sites of discussion, or at least at their margins. This allows for the formation of counter-publics via deliberation, whereby contestation can occur, and had actually often occurred in the case of minority-related issues, both with respect to other dominant deliberative circles and with respect to political insititutions proper.

Practical ways to enact delibeartion and participation into technology appraisal and policy-making have proliferated in the last thirty years or so. We can now say that a whole field of political science, hyrbidised with political philosophy, ethics and the social sciences, has matured around the elaboration of deliberative techniques. This is not the place to review them, nor to assess their effects on the individual issues they were used

to cope with. In the last chapter, however, I will produce some practical indications as to the implementation of deliberative arrangements for the governance of biomedical innovation. For the time being, it is importat to bear in mind that deliberative democracy stresses the *process* by means of which political decisions are arrived at. In an ideally participative process of deliberative opinion- and will-formation, individual preferences and values can be transformed, possibly – although not necessarily – leading to consensus on otherwise divisive public issues. Most importantly, deliberation is conceived to motivate participants "to resolve conflicts by argument rahter than other means" (Warren, 1995, 181).

Therefore, to conclude this section, I would stress once again that, to the extent that deliberation is not supposed to produce political stabilization if not of an ever-contestable sort, it is a source of legitimation for publicly binding decisions in a pluralistic society. However, deliberation that preceeds policy decisions, albeit not necessarily institutionally connected to them, may as well be unable to bring political confrontation and moral disagreement to a definitive closure. On the contrary, I embrace deliberative democracy as an account that is able to stress the necessity that a pluralistic society retains the capacity to discuss about divisive issues, and to resist the culturally and politically erosive consequences of the diversity of moral cultures that contemporary societies exhibit. It is thus crucial to understand that, in the case of biomedical innovation, deliberation and participatory technology assessement can play a legitimising role for policy decisions by rendering them more responsive to citizens' interests and concerns.

1.6 Towards dialectic integration

Let me know briefly recapitulate why I think that co-production and deliberative democracy might methodologically go together in a rather fruitful way.

To begin with, I have described co-production as a methodological account that is capable of appraising the critical role of discursive practices at deconstructing authority and thinking of possible alternatives to current political arrangements around science. The idea of public sphere, as described by Habermas and followers aims exactly at the same junction of discourses and contestation that, in the case of technological change, are not only possible but also appear desirable. However, I highlighted the inadequacy of STS analyses at providing sufficient normative guidance as to how this public sphere of discourse should be structured to make policy decision on technology democratically more legitimate. To this deficiency, I think deliberative democrats have interesting insights to offer as to the articulation of a truly open space for discussing innovation. On the other hand however, STS can support and complement deliberative democracy in watching out against the risk of essentialising the rational requirements of deliberation and discursive exchange.

Secondly, I think I have made clear that, in my opinion, STS has given a valid contribution as to the necessity for inclusion and participation of all stakeholders in the debate on science policy. I also said however, that excessive focus on problems of representation actually clouded the political vision of this discipline, thereby calling for a substantial increment in the attention paid to problems of legitimation. To this aim, I think deliberative theories have much to offer, as I showed above. Again, however, STS scholarship can provide deliberative accounts with a constant reminder of the always

imperfect nature of the Habermasian circuit that connects, or actually often fails to connect, the communicative power of public opinion with the institutionally shielded and culturally excluding mechanisms of public decision-making.

Lastly, STS, thanks to the co-productionist lens, has been able to detect the exclusivist premises and the authoritative outcomes of institutional design aimed at bringing conflicts about science to a decisional closure. This is in line with the idea that deliberation does not rest on universalistic aspirations to the optimal solution of policy debates. Rather, deliberation relies on the democratizing function of an open debate where opinions can freely form and circulate, with no *a priori* preclusions towards the provenience of discourses, the social position of discussants, or the nature of the topic under discussion. In this sense, political deliberation absorbs in advance the destabilizing potential of political conflict, thereby reviving a politically democratic environment where new divisive issues can be both anticipated and prepared for decision. The co-productionist lens however, is still able to deconstruct the political arrangements that emerge from necessarily imperfect forms of deliberation, thus highlighting the criticalities that the polity should organize to resolve.

The two components mitigate their respective defects complementarily. Furthermore they reinforce each other's commitment to understanding social and political agency, as well as power relations, as made of language, knowledge, evidence, and the institutional arrangements that allow their production and exchange. However, a bundle of deliberative theory and co-production, as I intend it, is not bound to fully integrate these two methodologies. Rather than forcefully imagining a seamless intermixing of the two, I see them in a constant dialectic interaction, one that is permitted by the features and commitments that they have in common, while at the

same time being kept in tension by their differences, thus leading to different divisions of labour according to the circumstances of the analysis.

With respect to biotechnological development, the two components of the bundle allow for conceiving innovation to be dependent on both interests and arguments, and on both the social and the epistemic resources that are available, thus avoiding both social and technological determinism. This outlook makes it thus possible to see innovation as an open ended political and technical process, rather than a linear trajectory of progress towards a land of promise and realization.

1.7 Democratic erosion

The necessity to bring together this hybrid methodological toolkit, however, has much to do with the kind of inquiry, and the kind of answers that I am after in this dissertation – my aim being to assess the impact stem cell innovation is bound to produce on the democratic culture of Western democracies. Although generalization are always difficult, and seldom useful, I think one can agree in characterizing the kind of risk that conflicts over biotechnology pose to democracies as, generally speaking, one of democratic erosion.

With that expression I want to signal the possibility that the cultural resources by means of which a polity gathers at formal and informal sites of discussion and collective action, are amenable to be consumed by the conflicts a democracy debates about. This is so because, as I have stressed above, decision-making, also in the idealized model of deliberative theories, recapitulates the discursive circulations and brings them to a closure. Political decisions, however, by no means have to represent a compromise

among the existing stakes and points of view. It is thus often the case, that, at the moment of public decision, one discourse becomes dominant over the others, albeit only temporarily, and thus manages to implement its reasons through legislation. These moments of closure, bring historicity into the rarefied image of circulating opinions and political wills, as arguments, moral commitments, and political ideals that flow around public issues give rise to concrete institutional designs. This is the moment when, for instance, the public disagreement about biotechnology runs the risk of becoming erosive. It is indeed necessary to recognize that a given policy or regulatory regime, once adopted, needs resources to be implemented and maintained, or as some say, socially reproduced. From the perspective of deliberation, this means that, as a first consequence of public issues becoming a matter of political decision, deliberation recedes to the background to leave room for actual policy-making. Public discussion may thus seem antithetic to the necessity to bring a debate to a closure, even if it was necessary to feed decisions with legitimating reasons. To the extent, however, that those policy decisions, unlike in the classical liberal framework, are not based on the capacity of democracy to channel full-blown universally acceptable solutions to political conflicts, the legitimation of those policies is not given once and for good. Quite on the contrary, policy decisions, so to say, have to remain unstable and open to further contestation, especially in the presence of appreciable degrees of epistemic and value pluralism that are typical of late-modern capitalist societies. The stabilisation of pluralism in matters of technological innovation is precisely what should be expected from deliberative and participatory exercises in the governance of technological change.

Recently, the debate on technology assessment (TA) has matured to the point of fully appreciating the virtues of deliberation with respect to pluralism and policy

accountability (see Chilvers 2008, 156 for multiple references, plus Vig and Paschen 2000, Guston and Bimber 1993, Renn 1999,).

This is not to deny that a participatory appraisal of technology, as well as deterministic outlooks on technological innovation, remains open to the influence of incumbent interests and unbalanced power relations – a characteristic that has been rightly termed "general sensitivity to framing" (Stirling 2008, 275). It has however to be stressed that deliberation foresees the open-ended character of public engagement as a feature that preserves the democratic culture from the erosive effects of moral disagreement over biotechnological innovation.

Technology assessment, therefore, may always remain "about closing down the formation of technological commitments" (*ivi* 278). Stirling rightly observed that, whether analytic or participatory, social appraisal [of this kind] cuts through messy, intractable, and conflict-prone diversities of interests and perspectives to develop clear, authoritative, prescriptive recommendations informing decisions" (*ibidem*). Scientific advisory processes, then, regardless the amount of deliberation they may endorse, generally lend themselves or, better, are generally expected by decision makers, to give way to "unitary and prescriptive policy advice" (*ivi*, 279).

But social appraisal of technology can indeed, and should, in genuine deliberative terms, be considered as a process that widens the agenda of the available technological options by including discourses, uncertainties and contestations. This is especially true of policies having to do with rapidly changing episodes of technological development, like stem cell innovation.

In those cases, the epistemic authority of some of the involved actors, and the institutional embeddedness of substantive moral commitments can indeed provoke the

marginalisation of alternative framings – as I will show in chapter 4. It should nowadays be notorious to policy scholars that, in those conditions, conflicts are more than likely to emerge. The latter usually proved extremely difficult to govern and cope with, and led to decade long legislative and jurisdictional battles. Deliberation and participatory exercises can thus counter-balance this tendency and indeed provide firmer grounds of legitimation to more accountable policy decisions. In the last chapter I will devote some specific analyses to the available deliberative tools as to their suitability to ease conflict and promote a pluralistic appraisal of cellular technology. Opening-up technological appraisal must thus prevail on closing-down policy advice, if democratic erosion has to be limited in its delegitimizing effects.

As it is evident however, notwithstanding deliberation and participatory technology assessment, politics will almost naturally try to limit the emergence of new disagreement through the *legitimate* exercise of what Habermas calls the administrative power (Habermas 1998). Nonetheless, a more inclusive political culture in the ordering of technological matters is certainly growing in Western democracies, and it is replacing worn-out technocratic paradigms of decision-making.

In recent years the notion of 'governance', as an alternative to 'government', has emerged in the political debate to indicate policy making efforts that take those dynamics into due consideration. Governance is supposed to mean the legitimate exercise of political and administrative power unaided by any effort at articulating a culturally hegemonic narrative around the implemented policies. This of course corresponds more to an ideal that to an actual form of democratic politics. However, I think that in order to manage the erosive potential of divisive public debates like those enacted by biotechnology, governance could be taken as a model for letting dissenting discourses free to circulate and re-emerge at other locations in the future. From this perspective the

main forums of democratic culture are, again, not necessarily coincident with the state and its representative institution. Rather, as in the case of middle democracy (see *supra*), a deliberative outlook of politics allows us to see new spaces and new places as emerging forums for sustained and democratic public discussion of biotechnological innovation.

Given current efforts at bringing stem cell to the clinical side of development, how are Western public spheres to react to the ethical challenges that these efforts imply? Is it possible to anticipate those challenges and prepare for their management rather than waiting for their divisive effect to manifest? And if so, how could this be realized? What is the nature of the divisions that stem cell innovation can produce, and what is the place of science with respect to them? Which kind of democracy is possible around the evolving streamline of biotechnology? What are the risks that democratic polities have to face when divisions arise about the use of biotechnology? These questions have not been taken at face value by the good old debates on the moral status of the embryo that figured as the main site of dispute on stem cell research up to a recent past. With the tools that I have outlined above, I thus aim at attempting to at least take those questions in due consideration.

1.8 Ordering the subject matter

This dissertation draws on the realisation that we have now reached a point where what has been imagined about stem cells is beginning to be translated into practice, albeit slowly and watchfully. From this point of view, stem cell research today is uncontrovertibly a site of innovation. What is being introduced through such innovation

trajectory however, is not yet another inert technological apparatus, or at least it cannot be fruitfully interpreted as such.

I will show how stem cell innovation is presently calling for a re-interpretation of existing discursive resources as well as for producing new ones in order to construct, along with knowledge and experimental abilities, the political and legal order that will allow stem cells to circulate from and into human bodies. In this sense, innovation is as much scientific and technical as it is social, political and, ultimately, cultural.

The complex interaction of regulatory and scientific order that takes place at the junction of stem cell innovation with clinical science is bound to be apparent along two axes of such developments: the research model and the translational model of stem cell science. As to the research model, the ways in which the fabrication of pluripotent cells and their use at the clinical level are regulated are emerging as major sites of governance innovation. As I will show in chapter 3, the shifting of stem cell science towards clinical application is being associated with an evolving culture of public oversight over scientific research for which no wild cards exist for any given instance of scientific innovation.

Therefore, as I will show in chapter 4 speaking of the translational model of stem cell innovation, these issues have direct repercussions on how stem cell therapies are being imagined, and how the boundaries of permissible experimentation are negotiated with the public and within the scientific community. It will thus become apparent that stem cell therapies pose new challenges to the existing regulatory frameworks on medical experimentation on human subjects, thus calling for some major reconsiderations on the use of notions such as risk and safety.

Moreover, looking at those emerging dynamics, I will primarily aim at using the deliberative lens to see how an ultimately democratic culture of discussion might be

preserved in the presence of the high stakes that these developments imply. Therefore, I will show that the problems of both the research, the business and the translational model of stem cell innovation, albeit discussed in specialized academic and professional circles, are sites where new tensions are arising whose erosive potential must be stabilized. In chapter 5 I will advance a proposal in this direction so as to conclude the dissertation with the effort of stimulating the emergence of an academic and public debate on those issues.

My general aim here is definitely not that of guessing whether or not stem cell-based medicine is going to make its way through to become a successful technology. I will instead focus on specific controversial regulative issues that might play a role in defining the shape of regenerative medicine in the future and, in turn the shape of the public sphere that will have to cope with those controversies. In this respect, this is an inquiry into the political conditions of medical innovation in the field of stem cells.

So let us start, in the next chapter, by illustrating the content of the promise of stem cell medicine.

Chapter 2: Stem cell attractions

In this chapter I will explain what the promise of stem cell science amounts to. My analytical aim here is to illustrate the promissory character of stem cell innovation.

To begin with, I will show that major improvements are expected from the possible application of stem cells to the construction of more precise disease models and drug screening libraries (2.1). Furthermore, I will explain what is intended for regenerative medicine, and how stem cell research and application is relevant to it (2.2). I will then illustrate how the study of stem cells can influence the development of medicine towards more personalised therapeutic approaches (2.3). Finally, I will restate how issues of governance are relevant to these various trajectories of innovation (2.4).

In so doing, I will draw on the existing scientific literature on the envisioned applications of stem cell research to medical practice. However, I will not attempt any estimate as to the likelihood of this or that particular application to ever reach the patient's bedside. Given the fact that most of these attempts are still in their infancy, I will furthermore remain neutral as to the degree of clinical development of the possible applications that I will briefly review in this chapter.

Stem cells are generally defined operationally, that is to say, stemness is attributed according to a cell's capacity to perform two fundamental biological functions: self-renewal and differentiation into more mature tissue types. This definition has given rise to a complex, and often not uniform (Brivanlou *et al.* 2003; Maherali and Hochedlinger 2008; Daley *et al.* 2009; Ellis *et al.* 2009; Müller *et al.* 2010), experimental apparatus to probe and certify cellular stemness. Such an apparatus allows room for a diversity of stem cell derivation methods. The cell lines that go under the label of stem cells therefore comprise a variety of entities exhibiting the hallmarks of developmental competence as well as self-replication ability at varying degrees.

Stem cells are naturally present in the developing embryo, as well as in adult organisms, where they have the important function of replacing some kinds of bodily tissue upon specific physiological or pathological circumstances. Those stem cells that reside in fully formed adult organisms generally possess lower degrees of developmental competence than their embryonic progenitors. Moreover, it may take invasive medical procedures to yield just small quantities of them from live human bodies. Presently, adult stem cells can be safely harvested by direct isolation only from bone marrow, umbilical cord blood, skin and adipose tissues (hematopoietic and mesenchymal stem cells). Stem cells isolated from the early blastocyst, instead, are pluripotent, meaning that they can self-replicate indefinitely and can be instructed to differentiate into derivatives of the three germ layers *in vitro*. The distinction between embryonic and adult stem cells, however, is not just a biological one. This line of separation indeed organised the political separation of supporters and adversaries of different approaches to stem cell research. On one side of this divide sit the promoters of stem cells of embryonic origin, whose derivation implies the destruction, and in some cases the previous creation, of human

conceptuses. On the other instead, reside those who judge such methods ethically unacceptable and thus sponsor the allegedly less problematic field of adult stem cells.

Thus far, embryonic stem cells have generated a good deal of ethical disagreement ever since their first derivation in 1998. The issue of the moral status of human embryos, whose creation and destruction are required to derive human embryonic stem (hES) cells, occupied the mind and writings of a large part of the bioethical community, and attracted the interests of many social scientists. Moreover, also the popular media dedicated much more attention to science around stem cell-related topics than they would have done otherwise. Science itself, on its part, devoted an ever increasing wealth of financial and human resources to stem cells, in the effort of gaining molecular knowledge about them, and in constant view of possible medical applications. To mention but one data about the amount of expectation stem cells have generated, it is sufficient to look at the case of California. The California Institute of Regenerative Medicine (CIRM), a State-owned funding and research institution created in 2004 with the aim of fostering the translation of basic stem cell research into deliverable therapies, received an initial endowment of about $3 billion over a ten year-period to fund stem cell research at "California's universities and other advanced medical facilities throughout the state" (Proposition 71). Two considerations are in order here to understand the import of this fact. First, CIRM's budget for stem cell research, as pointed out by Daar and Greenwood (2007), is comparable to that of the Human Genome Project. The latter received a total of $3.8 billion in fifteen years, from 1988 to 2003 from the Department of Energy and the National Institutes of Health. Indubitably, the complete sequencing of the whole human genome epitomises a moment of crucial cultural importance in the history of human civilisation, other than being a watershed event in the history of scientific knowledge. On this project the US government imagined to build the

second wave of development for medical biotechnology and, possibly, to create the conditions for future innovative therapies. The budget of the Californian stem cell research initiative was approved by the people of California through a referendum on a constitutional amendment named Proposition 71 in 2004, for a public expense figure that is comparable with that of the Human Genome Project. This reveals how much stem cells can elicit public expectations on the potential innovations they may bring about. Moreover, the fact that CIRM was created and allocated resources via a constitutional amendment, enacted by California voters through public consultation, certifies the extent of public endorsement that stem cell research is able to gain within the public. As a matter of fact however, expectation and opposition are indeed both present within the public debate concerning stem cell research and its possible applications to combat human diseases. Instances of public contestation of stem cell research are countless. To mention but a recent one, we can for example recall the opposition to stem cell patents in Europe. A decade-long judicial battle over stem cell patentability in Europe saw individual scientific research groups facing the opposition of a large and fairly representative panel of parties, including three EU member states (Germany, Italy and the Netherlands) and non-governmental organisation (NGOs) such as Greenpeace.

With these considerations in mind, let us now review the directions that stem cell translational research is pointing at to envisage the possible future development of new stem cell treatments. In what follows I will try a systematic, albeit inevitably incomplete, overview of the current directions of applicative stem cell research. Furthermore, I will outline the main points of concern that the debate on stem cell science is focussing on, with respect to regulatory difficulties and ethical problems that those kinds of research are likely to elicit. This initial overview will function as an entry point to the issues this dissertation will take up subsequently. To put order into the coming review of possible

stem cell applications, I have divided them in three main areas: drug screening and disease models, regenerative medicine and personalized medicine.

Obviously, trajectories of biomedical innovation are not easy to anticipate. With stem cells then, predictions are even harder than normal. This is due to specific peculiarities of stem cells as material objects and as objects of study. Indeed, the biological variety among different stem cell types, stem cell lines, and variously obtained stem cell derivatives makes it extremely difficult to speak of the future of stem cell medicine because exactly which kinds of stem cell will eventually prove most valuable in therapy and other patient-oriented operations is virtually impossible to predict.

Moreover, as to the regulatory scenario surrounding stem cells, it has to be said that it has always been unstable, and continues to be open to change as political initiatives unwind and judicial controversies are decided over the possibilities and the limits of stem cell research. Furthermore, regulations are influenced by the ongoing scientific efforts of molecular and mechanistic characterisation of new pluripotent entities that laboratories worldwide continue to obtain.

2.1 Drug screening and disease models

A distinctive feature of stem cells, is the possibility of retaining the genetic characteristics of their organism of origin. To begin with, stem cells of adult origin possess the same genetic material of any other somatic cell in the donor's body. They can thus be matched to the same individual in a therapeutic context, although they may present problems of immunocompatibility with recipient patients in heterologous settings. Moreover, they have another important limitation that has to do with their reduced

differentiative potential: adult stem cells are unable to differentiate in all the derivatives of the three germ layers like, instead, embryonic stem cells can do. Human embryonic stem cells, instead, are pluripotent, indicating that they can give rise to all somatic cell types of adult organisms. Furthermore, human embryonic stem cell lines derived by somatic cell nuclear transfer (SCNT) are genetically identical to the somatic cell donor, thus permitting a targeted to patient derivation upon clinical or research necessity. SCNT, however, proved technically problematic and thus prompted research groups to look for alternative methods to obtain pluripotent stem cell. Induced pluripotent stem (iPS) cells, obtained by ectopic expression of key transcription factors in somatic human cells (a process also referred to as reprogramming) are now considered a valid counterpart of hES cells and a possible alternative to them in the clinical and research contexts (Takahashi and Yamanaka 2006; Takahashi *et al.* 2007). IPS cells just like hES cells proved able to give rise to derivatives of all the three germ layers, but they are considerably easier to obtain from an experimental (as well as from and ethical) point of view. Importantly, also iPS cells retain the same genome of the person whose biopsied cells underwent reprogramming. These features immediately gave rise to the realization that stem cells obtained from a patient should exhibit the same diseased characteristic of the original tissue at least at the genetic level. It was thus tempting for scientific groups working in molecular medicine, to establish pluripotent cells from diseased subjects (either animal or human). Those cells can then be differentiated into mature somatic cells, generally of the type that the disease is supposed to hit. It is so possible to obtain copious *in vitro* cellular cultures that supposedly recapitulate the diseased cellular phenotype of the patient, thus representing what has been called a “disease in a dish” (Wu and Hochedlinger 2011). Scientists can in this way create in vitro models of human diseases, with the aim of studying them, so as to hopefully learn more on the molecular

mechanisms that underlie the disease, or in order to test on this abundant material entire libraries of potential drugs, in the hope of finding those that are able to interfere with the disease, or to restore the normal cellular phenotype.

A number of stem cell-derived disease models have already been established for neurodegenerative diseases like Parkinson, Huntington and amyotrophic lateral sclerosis; likewise, as to blood related pathologies, many cellular disease models exist of Fanconi anaemia and Fragile X syndrome; also cardiac and vascular conditions like LEOPARD and Timothy syndromes are now observable through in vitro models, like also pancreatic (Type 1 diabetes) and hepatic illnesses (for complete reference see Wu and Hochedlinger 2011).

Specific technical and regulatory hurdles however constrain the full development of cellular models for human diseases. To begin with, not many human diseases exhibit a clinically relevant phenotype at the cellular level only. Moreover, only a subset of human pathologies has a cell-autonomous nature. The complexity of some prominent human disorders may therefore be scarcely captured by *in vitro* models. Furthermore, the heterogeneity of human disorders might question the reliability of disease models when derived from a small number of initial donors. Indeed, efforts at replicating the establishment of diseased cell lines, might reveal that a single disease actually comprises many different sub-forms, thus calling for a more refined stratification of donors. If this is in itself a worthwhile result, it adds a further layer of complexity to the fight against human disease.

At the regulatory level, the use of cellular models might be problematic in at least two respects. First, donor tissue is stored, manipulated, expanded and circulated to such an extent by molecular biologists, and its use may give rise to such unforeseen results

that the initial consent of the donor cannot assure control over all the possible future uses of the samples. As large repositories of human diseased cell lines expand, the management of the biomedical information they contain for research and clinical purposes thus becomes more pressing. Second, the outcome of drug screening on animal disease models, might not provide sufficient information about toxicology and efficacy to immediately start reasonably safe clinical studies. This problem is even more acute in the case of *cellular* disease models, given the fact that they are unable to fully recapitulate the effects and side-effects of a drug at the organismic level.

It is also worth noticing that, contrary to commonly held assumptions in the academic community, embryo-related issues do not nearly exhaust the scope of the potentially problematic consequences of stem cell research. The very notion of consent, originally brought into the realm of medical practices to avoid clinical trials being conducted on human subjects against their will, seems bound to be re-organized around the new uses of human tissue that stem cell science is able to make possible. The scope of consent extends to a variety of scientific procedures that, like in the case of diseases in a dish, happens at sites far removed from the patient. Nonetheless, at the same time, the content of consent seems to shrink or even exclude forms of extensive control by the initial donor. Furthermore, in the case of drug screening, large revenues may result from these initial experiments on existing small-molecule libraries. It is therefore desirable for the involved research groups and companies to enforce in advance rules of appropriation for those revenues that, to my knowledge, in all cases involve the exclusion of the donor-patient from the potential financial benefits of drug discovery activities. The creation of a practicable infrastructure to allow the uncontested use of stem cell techniques in modelling human diseases is thus dependent on the emergence of a favourable civic environment around the practices in question.

2.2 Regenerative medicine

Regenerative medicine is one of the articulations of the new medicine that is more frequently associated with the development of stem cell science. Albeit not entirely original, the idea of restoring human tissues' impaired functioning regained momentum as science proved able to experimentally control the proliferative and differentiative fate of human cells in vitro. Thus new manipulative abilities tempt biomedical researchers to probe how stem cells could be harnessed in vivo, to restore the functionality of diseased bodies. In truth, the rationale for taking this therapeutic direction is not entirely new. Well-known early examples of regenerative medicine are blood transfusions, organ transplantations, and bone marrow grafts for leukemic patients. The latter technique was actually the first stem cell therapy to successfully bridge the gap from the bench to the bedside. However, one main difference between these early examples of regenerative medicine and what stem cells might do in terms of bodily regeneration needs to be highlighted. Blood, organs and bone marrow are transferred from one body to another following relatively minor manipulations, apart from those handling procedures, like refrigeration for example, that are necessary to keep them alive while being transported from the donor to another recipient body. The idea of regenerative medicine that stem cells can contribute to build, however, generally means more than just replacement of dysfunctional tissue with the same tissue-type taken from a compatible donor. The displacement of human cells from one body to another will be technically mediated by molecular-level manipulations that transform an initial tissue into the desired kind of entity that the receiving patient needs. Now, although the technical feasibility of such manipulations has in principle been already shown in model organism such as mice, these processes are more difficult to control than tissue displacement from body to another.

Let us now try to be more specific as to what regenerative medicine is meant to be by looking at a definition that captures its imagined potential in a relatively condensed way.

> "*Regenerative medicine* is an interdisciplinary field of research and clinical applications focused on the repair, replacement or regeneration of cells, tissues or organs to resort impaired function resulting from any cause, including congenital defects, disease, trauma and ageing. It uses a combination of several converging technological approaches, both existing and newly emerging, that moves it beyond traditional transplantation and replacement therapies. The approaches often stimulate and support the body's own self-healing capacity. These approaches may include, but are not limited to, the use of soluble molecules, gene therapy, stem and progenitor cell therapy, tissue engineering and the reprogramming of cell and tissue types" (Daar and Greenwood 2007, 181).

Although other definitions of regenerative medicine exist in the literature (Petit-Zeman 2001; Haseltine 2003; Mironov, *et al.* 2004), the one I reported here enjoys the virtues of brevity and, to an acceptable extent, comprehensiveness. Before entering into some more details about what effective possibilities this quote might refer to, let me comment a bit on what I think is worth highlighting in the proposed definition. Nearly every word in the above definition points at features of regenerative medicine that make it look novel and innovative with respect to the past.

The first innovative feature is the tight coupling of research and clinical application. The traditional (and overstated) division between basic and applied research is blurred, to the point of allowing room for the emergence of a new interdisciplinary

field. As a consequence it is currently possible to observe the flourishing of departments and schools, institutes and departments of regenerative medicine worldwide. This feature has a counterpart in the proliferation of interdisciplinary programmes and academic degrees dealing with the fundamental regulative issues raised by the coming of age of regenerative medicine and other affiliated new articulations of medicine.

Secondly, not only regenerative medicine aims at replacing non-functioning bodily parts, it points at repairing and regenerating. What is meant with repair is the possibility of using technologies such as stem cells to intervene on wounds produced by external traumas or by internal failures, like in the case of spinal cord injury or myocardial infarction respectively. Yet another possibility for repairing diseased bodies is to engineer cells before introducing them into patients in order to confer them a phenotype that might benefit the patient, as it was the case with modified β cells administered to type-1 diabetic patients (Emamaullee *et al.* 2005). With regeneration instead, what is meant is the possibility of intervening on the adult stem cells, already present in the human body, by pharmacologically stimulating their niche, where they generally reside in a state of quiescence thanks to a delicate homeostatic equilibrium (Rafii *et al.* 2002; Scadden 2006; Adams *et al.* 2007).

Even if the use of 'repair', 'regeneration' and 'replacement' is not uniform in the biomedical literature, it is important to stress here that regenerative medicine stretches onto a variety of diseases and conditions, from congenital defects to disease and trauma. Functional restoration is therefore the aim of treating a continuum of forms of impairment, not rigidly mapping onto the clusters of medical specialisations.

The most innovative feature of regenerative medicine however, as it is accounted for in the proposed definition, is the idea of converging technological approaches. To an

extent that is not possible to ignore, regenerative medicine favours the emergence of new technological platforms, such as stem cells for example. By technological platform I mean a family or bundle of biotechnological tools and clinical hypotheses grouped around one core entity (in our case, stem cells) that has yet to be developed into deliverable applications.

This notion owes to Keating and Cambrosio's idea of biomedical platforms(Keating and Cambrosio 2000; Keating and Cambrosio 2003). However, my interest in the emergence of stem cell medicine is less concerned than theirs with the historical upheaval of stem cell science as an experimental system with roots in neighbouring scientific fields, and built up on the material and institutional characters of novel 'epistemic things' (Rheinberger 1997).

What the idea of platform, as I intend it, is supposed to capture, is the fact that the technological trajectory of stem cells is not decided in advance, but is instead being developed in parallel to the process of scientific characterization of the core entity itself. Like in the case of other recent technological platforms (e.g. recombinant DNA technologies), it will thus be difficult to predict, in the case of stem cells as well, exactly what type of future application they will enable, which kind of disease they will most frequently be used to combat, which kind of industry, if any, will profit from them, and so on. In this respect, commentators have seen a line of connection between stem cells and the Human Genome Project, beyond the budget they were endowed with, highlighting the fact that both lend themselves to be seen as forms of "scientific inquiry whose benefits will emerge slowly and incrementally" (Dresser 2010). I will elaborate more on this feature in the course of the dissertation. As more information and analyses will accumulate about how stem cell innovation, at the present stage of its development, is being imagined, I will return to the notion of technological platform. The latter, I reckon,

captures the trajectory of stem cell innovation in a more convenient way than other, more established concepts such as that of 'technological zone' (Barry 2001; Barry 2006). The difference between 'platform' and 'zone' lies in the nature of the technological phenomenon that the two expressions are intended to capture. With technological zones', scholars have referred to families of products that, in one way or the other, are related to one specific kind of medical application. A typical example of a technological zone is tissue engineering. Engineered human tissues can come in a variety of forms and instantiations, but they are all designed to replace a part or a function in the human body. Technological platforms, instead, refer to an innovation trajectory that revolves around one single entity, but lends itself to a multiplicity of possible applications, both medical, diagnostic or laboratorial. The field of stem cells, as I see it, is thus more appropriately defined as that of a technological platform that is evolving into as yet unpredictable applicative directions.

The open ended character of stem cell innovation as a biotechnological platform, also surfaces in the above definition of regenerative medicine, when the latter is said to rely on both existing and newly emerging technological approaches, purportedly converging on stem cell as an attractor-innovation. Therefore, the list of possible vectors to translate stem cell knowledge to medical practice in not limited to cell therapy proper, but stretches to chemical drugs, biologics, functionalised materials and other possible applications that might, and will most likely spur out of the science of stem cells.

As to the possibilities of medical translation, a number of proof-of-concept studies and early-phase clinical trials have already indicated the imagined future of the new stem cell medicine. Cell therapy, consisting in infusing patients with cells at specific bodily locations, is generally thought to be the main avenue of stem cell science clinical application. A number of recent studies provide support for this assumption. Pioneering

research efforts are currently being devoted to previously incurable and strongly debilitating neurodegenerative conditions, for example in the case of Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis (Lindvall, Kokaia, and Martinez-Serrano 2004). Preliminary studies on animal models suggest that stem cells could be used to restore brain functions that conditions like those just mentioned generally disrupt, thereby restoring the hope for patients to contain the loss of crucial cognitive capacities, as well as to re-acquire the control of their bodily movements. Furthermore, also other conditions affecting patients' autonomy and wellbeing by impairing their capacity to move, like muscular dystrophy, seem amenable to stem cell therapy (Sampaolesi *et al.* 2003).

Furthermore, evidence is accumulating in favour of a possible beneficial utilization of stem cell therapy in type-1 diabetes (Lechner 2004) and autoimmune diseases (Marmont 2000), as well as in type-2 diabetes (Soria *et al.* 2000) and in other highly spread conditions often related to metabolic syndrome like stroke (Lindvall, Kokaia,andMartinez-Serrano 2004).

Cardiac infarction (Dimmeler, Zeiher, and Schneider 2005; Segers and Lee 2008), spinal cord injury (Keirstead *et al.* 2005), and wound regeneration are yet other examples of possible fields of application for stem cell therapy. Moreover, among the most promising targets of stem cell-based regenerative medicine, some squamous epithelium disorders can already be successfully treated with stem cell therapy. In particular, corneal regeneration by injection of corneal epithelium cells from the uninjured eye of the same patient proved an effective treatment for eye lesions and burns (Pellegrini *et al.* 1997; Rama *et al.* 2010).

Moreover, in principle, cell therapy could also be administered to patients through previously decellularized tissue scaffolds, as recent studies demonstrate. Among the most remarkable success in recent stem cell-related medicine, Macchiarini and colleagues recently implanted a tissue-engineered trachea functionalised with mesenchymal stem cell-derived chondrocytes obtained from the patient in a woman with a bronchial disease (Macchiarini *et al.* 2008).

To the same aim, research groups have also deprived body parts of their cellular content, to subsequently seeded them with cells grown in bioreactors. This procedure results in the cellular functionalization of bioartificial organs that successfully engraft and function in animals (Ott *et al.* 2008; Ott *et al.* 2010; Petersen *et al.* 2010; Uygun *et al.* 2010).

As a matter of fact, with few exceptions that I will deal with later on in chapter 4, most of the possibilities I described here proved feasible at the level of proof-of-principle studies only. This means that only few systematic clinical studies to test safety and efficacy of stem cell therapy have so far been undertaken on large enough cohorts of human participants. Therefore, evidence for stem cell therapy as a doable medical practice mainly comes from animal studies and/or from preliminary attempts on small number of human subjects.

Moreover, many of these studies showed that stem cell-based regenerative medicine will have to face serious safety problems. The main safety hurdle to stem cell clinical translation is the alleged tumorigenicity of stem cells. The more a cell possesses self-renewal ability and differentiation potential, that is to say, the higher a cell sits in the differentiative hierarchy, the more likely it is that it will give rise to uncontrolled growth events after implantation in patients' bodies. Although this needs not necessarily be the

case, a number of studies in animal models as well as early experiments with brain stem cell-grafts show that this issue has to be taken into careful consideration. This is a sticking point for stem cell innovation even if what researchers try to inject are fully differentiated cells originated from less mature progenitors. Presently, purification techniques are still not 100% reliable, and it may therefore happen, for instance in the case of pluripotent embryonic stem cells, that teratogenic cells end up in the patient together with more mature – and allegedly safer – ones. Obviously, such an issue is not only a technical one. The scientific community, other that establishing safer ways to conduct cell therapy, will indeed have to engage in extensive discussions and negotiations with both stakeholders and regulators in order to establish thresholds of ethical acceptability for stem cell clinical trials that might imply such serious safety concerns (more on that in chapter 4).

In the light of these risks, both scientists and regulators have so far been rather careful and slow-paced in attempting and approving of stem cell therapy clinical research. The obvious safety concerns that such therapeutic approach elicits are therefore resulting in a generally cautious attitude of all relevantly involved actors to wait for credible proof-of-concept studies before daring to enter long and costly regulated pipeline of innovative cellular product development. As a matter of fact, early attempts at developing new stem cell therapy are decisive for the future of the whole field. Major failures in terms of safety are likely to be viewed as ethically disappointing and publicly difficult to justify, thereby potentially causing a crisis of public trust and support towards the field of stem cell regenerative medicine as a whole. Public support is an asset that cannot easily be acquired: it has to be deserved and maintained by showing that the reality of stem cell research actually fits into the ideal promises of the new medicine. In this respect, safety, even more than efficacy, is of the utmost importance. The value of safety and efficacy are however challenged not only by the intrinsic risk of, say, pluripotent cells being

technically difficult to control. The scientific community is indeed extremely worried about unscrupulous clinics around the globe offering allegedly experimental new stem cell therapies to desperate patients without neither the necessary ethical safeguards nor the desirable methodological rigour. Fraudulent attempts at selling unproven treatments, allegedly comprising stem cell concoctions, gave rise to a phenomenon that was labelled stem cell tourism, whereby many hopeless patients end up travelling to distant clinics in South-America or China in order to obtain expensive. I will come back to this problem in chapter 4, when, besides reconstructing the image of the stem cell research subjects that is emerging in the debate on stem cell tourism, I will discuss how the stem cell community itself, through a remarkably organized exercise of boundary construction, is indeed acquiring a political identity through patrolling the demarcation between acceptable and unacceptable therapies resulting from the phenomenon of stem cell tourism.

2.3 Personalised medicine

The idea of personalized medicine attracted the attention of academic circles in the last couple of decades. I take the expression 'personalized medicine' to encompass the scientific undertakings devoted at reducing adverse drug reaction, on one side, and at customizing clinical treatments to increasingly stratified classes of patients, on the other (Hedgecoe 2004; Woodcock 2007; Sturdy 2009).

The hopes of personalized medicine channelled a good deal of public hype. As a result, Western societies are now about to endorse a colossal cultural enterprise: as they start to take seriously the idea that individuals get ill in unique ways, and are thus entitled to be cured in unique ways, they are consequently bound to redefine the terms of the social arrangements that so far have characterized the provision of health care. At the

present stage of sequencing and genomic analysis techniques, genetic profiling is being offered over the Internet without medical intermediation, thus re-configuring potential patients as individual consumer of medical technologies (Curnutte and Testa 2011). But genetic sequencing is also on the verge of becoming an increasingly common practice in national health care systems[3]. Moreover, interesting correlations between individual physiological parameters and response to treatment are being gathered, thus paving the way for increasingly tailored medical approaches (Protani, Coory, and Martin; Ewertz *et al.* 2011). Personalized medicine thus envisions clinical practice to incorporate targeted-to-patient therapies that might prove more effective and less prone to adverse reactions, than those established by more traditional approaches.

In the anticipated future of personalized medicine, people may enter into contact with health personnel before any symptom will even arise. Their genome, epigenome, RNA, proteome and metabolites, according to the most prophetic proponents of this medical future will be analysed by means of emerging new high-throughput technologies (Hood and Friend 2011). The information so retrieved, coupled with medical records and environmental information will be compared with existing databases to look for the occurrence of medically relevant characteristics. The therapeutic intervention might thus begin before the patient presents the phenotypically visible signs of being ill, thus configuring the rather oxymoric figure of a healthy patient. These conditions imply a proactive kind of agency on the part of the healthy patient who will access screening facilities on the basis of her familial history, the environment in which she lives and her individual attitudes towards prevention. On the part of the medical infrastructure, genetic screening can either take place in regular clinics or in privately-held dedicated centres.

[3] The PHG Foundation has recently issued a report containing recommendations to the British National Health Service as to how to integrate whole genome sequencing in the standard practices of health care provision (Wright *et al.* 2011).

This, in both cases, entails the existence of specialized personnel who will be able to perform the tests, retrieve the information, communicate it to the patient and pave the way for the medical intervention proper. It is therefore evident that professional boundary work is likely to happen, and that setting up these roles might even be conducive to some controversy and professional power game. Treating, so to say, the asymptomatic patient will start once the screening reveals that a pathology is likely to arise in the future, but the nature of such intervention by no means must be similar to the actual therapeutic strategy now adopted to tackle the disease. This means that, from a technical point of view, tailored pre-therapeutic interventions will have to be devised. It is furthermore probable that those interventions will address the lifestyle of the patient, or her working environment, with an intensity that is way beyond what is currently being done in those areas.

A massive reconfiguration of the established social practices that currently surround traditional medicine, may also come from the interaction of personalized medicine and stem cell science. In the light of the more or less probable onset of given medical conditions, a healthy patient can for instance decide today to harvest and store bodily tissues for future uses. In this sense personalized medicine comes to coincide with regenerative medicine. Among the tissues that it will be possible to store, adult stem cells, but also biopsies may well be used as a reservoir for tailored-to-patient cell derivation. Such practices are already spreading today as the increasing availability of cord blood banking facilities testifies. Two considerations are in order here. First, the idea of privately owned stored tissues is antithetical to the narratives of generosity, altruism, solidarity and mutuality that characterize the circulation of spare tissues and organs in medicine today. Blood and organ donation, for instance, have grown together with a strongly charged moral discourse about the value of making one's body function as a

healing source for the diseased bodies of stranger fellow-citizens (Waldby and Mitchell 2006). With private banking, this narrative reaches a dead end, and a new, equally convincing one should supplant it in order for these new practices to really become the case. With this consideration we come to a second point about personalized medicine. Stem cell innovation, as I have just characterized with respect to the purposes of personalization, along with an augmented concern for pre-symptomatic patients, transforms the social role of the latter into one of consumers rather than of serviced citizens bearing a right to a healthy status. As a matter of fact, private companies are already offering personalized genetic services through the Internet, thus bypassing the intermediation of the medical profession, the regulation of the state and, even more so, the public discussion on the desirability of those changes (Curnutte and Testa 2011). This switch towards the consumerization of future patients is thus likely to determine the attitude of consumer-patients towards the use of their own bodily parts with respect to the personalized therapeutic possibilities that stem cell therapy might offer in the future.

These transformations are major ones[4]. They can drastically change the face of future medicine, by reshuffling the boundaries between medical and non-medical, health and prevention, and by configuring the emergence of new modes of agency that supersede the present layout of the doctor-patient-state relationship. These changes should thus be the object of careful deliberation within communities that are bound or even simply likely to embrace it. Such discussions however, do not seem to be prominent in the public debate, although many academics and technology specialists have already been engaging with this topics for a few years.

[4]For a general consideration of the ethical, legal and social implication of biomedical innovation in th field of personalised medicine see: Møldrup 2000, March, Cheeseman, and Doherty 2001, Robertson 2001, Rothstein and Epps 2001, Issa 2002, Mancinelli, Cronin, and Sadée 2002, Robertson *et al.* 2002, Lipton 2003, Vaszar, Cho, and Raffin 2003, Hedgecoe 2004, Webster *et al.* 2004, Stoughton and Friend 2005, Burke and Psaty 2007, Sturdy 2009, McGuire *et al.* 2010.

Among the main challenges for the implementation of personalized medicine is the fact that, in order, for instance, for genetic profiling to be scientifically meaningful, huge numbers of people should consent to give away tissue samples, and medically relevant personal information. Before becoming consumers of personalized medicine, patients should thus become partners of scientific research in the gathering of the necessary information. The creation of large databases is therefore both a technical challenge and an innovation that requires support and endorsement by participants. The latter however, might rightfully be worried about the handling of incredibly sensitive medical data by companies, researchers and the state. It is thus possible to envisage that in order to make large rates of participation possible, some work will have to be undertaken to construct a credible consent infrastructure that protects donors while allowing scientists enough freedom to operate. Moreover, also the rules for sharing these enormous sets of data must respond to the expectations of both participants, be them healthy volunteers of patients approached in a clinical context, and researchers. It is thus clear that demarcation between research, profiling and therapeutic intervention, far from being a clear-cut distinction, must reach a reasonable degree of stabilization in order for personalized medicine to be possible.

2.4 New questions for the new medicine

To the extent that stem cell research and application happen to intertwine with the trajectory of personalized medicine, regenerative medicine, in vitro modelling, and innovative drug discovery, these areas of experimentation and imagination come to share the very same technical and societal challenges. Again, this process is characterized by apparent dynamics of co-production whereby the construction of the epistemic and technical resources necessary to bring about change into medicine and health provision,

are not separable from the effort aimed at making these innovation ethically credible and socially accepted.

The existing regimes of governability for medical research and health care provision have indeed incorporated societal concerns about privacy, consent, and autonomy and property at many levels. Furthermore also the productivity of research and the efficacy of medicine, found complex statutory definitions. However, in the light of the promise of stem cell medicine, in its various realizations and ramifications, it has become urgent to ask whether and how such infrastructure is ready to incorporate and stabilize the concerns raised by innovation that are now for the first time appearing at reach for science and society. In this complex scenario, the challenge of anticipating ethical criticalities that are already investing, and will most likely characterize the emergence of the new medicine, lays before us.

Some commentators are skeptical about the possibility that such innovations will leave the existing regulatory framework of research and medicine unchanged. Therefore, some are already starting to offer reasoned practical suggestions as to how this framework could evolve to became able to address the new challenges. Such proposals also include the idea to increase direct participation by all the relevant stakeholders in the discussion of the rules that will govern the uses and circulation of human tissues (Gottweis and Lauss 2010; Gaskell and Gottweis 2011).

In the next chapters I will thus track the emergence of this complex web of technical, ethical and political interaction with respect to three main aspects of stem cell innovation. Preliminary analyses of the current early stage of the new medicine indicate that major instances of moral disagreement and political instability are likely to arise with respect to:

Issues of research policy - How is the governance model of stem cell science changing in relation to its application to medicine? How can regulators influence the route of knowledge production in view of possible future stem cell therapies?

Issues of translational research: What challenges lay ahead of the incipient efforts of clinical researchers and regulators to test the safety and efficacy of stem cells on human subjects?

Issues of property and benefit-sharing - The boundaries of ownership and circulation of cellular entities derived and expanded in molecular labs and the biotech business model that forms around them give rise to critical questions: should stem cells be patentable in the first place? How can the construction of ownership barriers around stem cells be compatible with an ideal of serviceable science and just distribution of health care resources? Are the interests of biotech and Pharma companies prefiguring the future consumerization of stem cell patients and the commoditization of health services and biological materials[5]?

In what follows I will show how scientific governance evolved from the traditional delegation model, to state-centred initiatives to regulate embryonic stem cell research, to a shared-model of governance characterised by efforts at regulatory normalisation of stem cell clinical research, and competing framings of this technological trajectory.

[5] Ethically informed social science perspectives on these two topics can be found in (Henderson and Petersen 2002) and (Waldby and Mitchell 2006).

Chapter 3: Stem cell medicine and the transformation of scientific governance

This chapter is divided into two parts. In the first part (3.I) I will illustrate the governance model that emerged from ethical controversies relative to stem cell research. I will show how the latter represents a marked depart from a cherished mode of governance of scientific activities in Western democracies in the aftermath of the second world war. More specifically, I will track the emergence of a state-centred regulatory model in contrast with the so-called social contract for science. In the second part of the chapter (3.II), I will instead show how a new regulatory model is growing around early efforts at translating stem cells to the clinic. My general aim will be to analyse where stem cell innovation sits in such a complex scenario and what specific governance model is emerging to cope with its novelty. I will therefore introduce what I call the 'shared-governance' regulatory model – one that is currently setting a rather open-ended regulatory order for the utilisation of stem cells with human subjects.

Chapter 3 - Part I: The legacy of stem cell research

3.I.1 The end of the social contract

The relationship between science and politics has been the object of studies that are now considered classics (Bush 1945; Gilpin and Wright 1964; Price 1965; Lapp 1965; Lakoff 1966; Polanyi 1967; Merton 1973). An intense debate stemmed out of these classics, as to the evolution of such relationship in the last fifty years or so. Two prominent features emerged from this debate as characteristic of science policy in the second half of the XX century. First, in the period between the end of World War II and

present times, science governance – that is to say, the political handling of scientific activities both within the scientific community and with respect to the use of science for policy decisions – has not always remained the same. Notwithstanding being realized in institutional and industrial arrangements, the relationship between science and politics has changed over time within single countries and has, furthermore, given rise to a variety of governance cultures in different Western countries. It is indeed uncontroversial from this body of academic work that each State enacted its own governance strategy, thereby giving rise to a globally heterogeneous landscape of differently constrained research models. This feature has been conceptualized as the product of the culturally specific ways in which "a nation's citizens come to know things in common and to apply their knowledge to the conduct of politics", thus engendering distinctive "civic epistemologies" (Jasanoff 2005, 9).

Second, a major turning point for the articulation of the science-politics nexus is the rise of biotechnology in the Seventies. The majority of the historical accounts of science policy, although drawing on diverse interpretative schemes, end up acknowledging in the late Seventies-early Eighties a moment of rupture with previously established modalities of interaction between science and politics (Guston 2000, ch. 6).

In particular, the latter transformation has been understood as the end of the so-called social contract for science (Guston 2000, Ch. 2,3). At its very basics, such metaphor intends to capture the mutually supporting but independent relationship between the state, as a provider of funding to science, and scientists that, free form any constraints on the part of politics as to the direction of their research, would allegedly provide technical innovation thereby contributing to the growth of the nation, both in terms of economic value and of individual welfare. The social contract for science, as described in such schematic terms, is not just an arrangement between institutions (science and political

power), but responds to the deep cultural and political commitments of its creators. It is generally assumed that the putative father of the social contract is Vannevar Bush, an MIT engineer who, during WWII, had directed the Office of Scientific Research and Development. Under President Roosevelt's request, in 1945, Bush wrote *Science: The Endless Frontier*, thus inspiring the organization of US post-war science and the creation of the National Science Foundation – the US funding agency for natural and social science other than medicine, already sponsored by the National Institutes of Health. The main theoretical legacy of Bush's account is the Mertonian conception of the independence of science and politics, the sharp distinction between basic and applied science – a distinction that influenced the very institutional architecture of university-based science in the decades to come – and the reliance on the integrity and productivity guaranteed by the peer review system.

Those ideas gave rise to widespread realisation that technological development occurs in a linear manner and should thus be governed accordingly. A linear conception of technological change endorses the belief that if scientists are left free to conduct basic research, the knowledge they produce will automatically be taken up by commercially oriented industries, which will eventually develop it into marketable applications to the benefit of American consumers and economy.

A linear conception of technological change, as described by dedicated scholarship, thus entails that the only possible intervention on the part of politics into the pipeline of scientific research and technological development was on the amount of public money spent to feed basic research. Under the assumption that university scientists should be left free to perform basic science, and that knowledge so produced would be developed into marketable inventions by the commercial firms, this model reinforced the boundaries between politics, science and industry.

This classic model of the scientific estate (Price 1965) represented a blueprint for countries outside the US as well. As noted by Jasanoff, British research councils as well as Germany's publicly funded research networks, tacitly adopted these modes of governance for knowledge production and technological development (Jasanoff 2005, 225-6).

It was however on the terrain of both productivity and integrity that the social contract for science started to fade out. Scientific fraud and misconduct episodes hit the attention of a wider public in the early Eighties (Broad and Wade 1982; LaFollette 1992), when Democrat Representative Al Gore held famous hearings at Capitol Hill on fraud in biomedical research. This awareness resulted in the intensification of governmental oversight on research and in a progressive decline of public trust in the enterprise of science. Integrity became so troubling for the political infrastructure that supported science in the States, that in 1989 the NIH was compelled to install an Office of Scientific Integrity (OSI) "which in the course of its brief existence attempted through its policies and procedures to maintain the separation between politics and science that characterized the social contract for science" (Guston 2000, 88). A few years later, in 1992, OSI was replaced by the Office for Research Integrity (ORI), a boundary organization at the intersection of politics and science aimed at establishing procedures to avoid misdeeds, and at adjudicating allegations of misconduct (Guston 2000, ch 4).

As to productivity, the governance structure of science, based on the social contract that Bush had initially devised, and theorists like Polanyi had further elaborated (Polanyi 1967), suddenly fell apart in 1980. With the rise of biotechnology, the possibility of bridging the gap between basic science and the industrial application and commercial exploitation of scientific knowledge became ever more tempting. Moreover, given the

difficult economic conditions affecting the US in those years, American politicians began to look at scientific innovation as a potential driver for economic growth.

With the emergence of biotechnology in the Seventies, the latter thus came to be identified as a major driver of a national effort to reacquire global economic and scientific supremacy. Allegedly however, the social contract model did not contain sufficient incentives to make that possible, and the sharp separation between university and commercial science had to collapse in order to attract investments and lead to the formation of partnerships between universities and the industry.

To this aim, patent protection was finally introduced also for state sponsored research as in the Bayh-Dole Act passed in 1980. This put an end to the thirty-year long narrative according to which "the results of research supported by grants of public moneys should be utilized in the manner which best serves the public interest [which generally occurs] if inventive advances resulting therefrom are made freely available to the Government, to science, to industry, and to the general public" (Guston 2000, 118-9).

The direct contribution of the patent bill on American university-based research has been a matter of scholarly controversy (Mowery *et al.* 2001; Mowery and Sampat 2005). It was however with the introduction of the Bayh-Dole Act, that university labs became increasingly more connected with the emerging industry of biotechnology start-ups, as offices of technology transfer worked aggressively at the intersection of scientific research and industrial application. In this sense, biotechnology worked as a model for science at large, as to the necessity to abandon the linear model of technological development that the social contract had endorsed. The pervasiveness of such model, however, is testified by the Stevenson-Wydler Technology Innovation Act (1980), stating that

> «[m]any new discoveries and advances in science occur in universities and Federal laboratories, while the application of this new knowledge to commercial and useful public purposes depends largely upon actions by business and labor» (Senate and House of Representatives of the United States of America, 1980).

Stevenson-Wydler thus sings the departure from the linear model towards relevantly different regimes of governability for science production and technological development. This shift in the governance model is evident in the intentions of the Act to dismiss the linear model, declared right after as the text continues: "[c]ooperation among academia, Federal laboratories, labor, and industry, in such forms as technology transfer, personnel exchange, joint research projects, and others, should be renewed, expanded, and strengthened" (*idem*).

Analogous patterns of change from the social contract model to the explosion of biotechnology as both a science and an industry are detectable in Countries other than the United States, where the model of scientific governance also inexorably veered toward the construction of ever firmer bonds between universities and commercial companies.

Scholars have analyzed the features of the linear model by stressing that it did not require any coordinating activity on the part of sponsoring institutions and that the political community was not charged of the costs of incentivising scientists towards specific areas of research (Alic *et al.* 1992; Guston 2000, chapter 5). In this sense, the model employs a narrative that sees science and innovation as agents in a free market of knowledge and items of high scientific content. The market is stable enough to attain two prominent goals at the same time. First, it feeds consumers' demand without the need of

any steering activity. Second it gives rise to a stable innovation environment for new basic research to be carried out and for new technological product to emerge from such knowledge. The beneficial effect of such market dynamics is given for granted and remained unquestioned for decades.

The model however, obscures the cultural and power relations that the social contract for science harboured. In particular, it black boxed the embeddedness of knowledge and technology delivery into the capitalist mode of production in post-war America, with the social relations that this entailed and the peculiar construction of the consumer as the central subject of American politics. The narrative of the linear model helped to set science and technology outside of the public's eye, by providing reassurance as to the beneficial public effects of letting scientists and technologists do their job in relative isolation. This self-regulative character, I would add, installed science and technology production into a politically empty space, where scientific and technological accountability was not at stake, if not to the extent of re-stating how citizens and the nation would benefit from the race to technological development.

STS scholarship has played a major scholarly role in highlighting that, "[this] picture has contradictory implications for democratic accountability [as] in each country, governmental efforts to build closer ties between academia and industry opened rifts between the practices of science and the demands of democracy" (Jasanoff 2005, 227). Driven by this kind of interpretation, a number of scholars in the social sciences started to stress the democratic deficit of science and technology governance over the last thirty years. The distance between science governance and democratic legitimation, grew in the long years when science and technology flourished in isolation from public discourses about their content, their modes of production and, most importantly, their role in the context of the wider aims of the democratic polity.

Indeed, the end of the social contract for science, provided impetus for the social science to re-think the very foundations of the science-politics relationship, in a way that may take citizens values and expectations in due consideration. Most commentators see the end of the social contract as a precondition to such transformed political program and, in particular, stress the fading away of the linear model as the most tangible sign of this transformation. With reference to the 1980 Act on technological innovation, for example, Guston maintains that "[o]nly with the demise of the social contract for science [was] such policy, focusing on the elements of the innovation process other than research inputs, possible"(Guston 2000, 118). I would contest however, that the self-regulatory model of technological development no longer plays any distinctive role in the governance of scientific innovation today. As I will show in due course later in this chapter, albeit in a completely transformed political environment, market-inspired ideals of scientific self-regulation still play a part in the kind of boundary work that occupies biotechnological development today. In the end, claims to self-regulation are integral to the highly contested regulatory landscape of biotechnological research. It is true however that, in the face of the rather stagnant condition of biomedical innovation, the idea of politically coordinating the global race to new drugs and biomedical technologies is gaining consensus even within actors that are traditionally hostile to political interference like the industry and venture capital firms.

Stem cell research, on its part, has been the object of numerous nation-specific efforts to control moral disagreement. Mainly due to embryo-related concerns and to moral issues regarding cloning, States have tried to regulate the derivation of human ES cells ever since they first appear on the scientific market back in 1998. The regulatory arrangements that resulted from such efforts qualify as instances of revision of the social contract for science as well as of the linear model of technological development, even in

countries that ended up adopting legislation that was favourable to stem cell research like the UK.

Regardless of the content of legislative initiatives taken to regulate the derivation of hES cells, and regardless of the kind of negotiations that gave rise to these complex regulations, all these attempts show a common feature. The morally problematic character of stem cell research, so to say, emerged as a distinctive feature of this kind of science. States in the West abandoned the idea that the production of science was by no means to become a matter of political initiative, and decided to intervene on the ways stem cell science was performed. As a matter of fact however, the availability of research funding was used as a leverage to channel the content of scientific research towards one direction rather than another. In the years of the social contract for science, political awareness had indeed grown regarding the importance of public money to the scientific enterprise. By the time of the early episodes of political control on the use of foetal tissue for research however, the idea that, once funded, science could not, and should not be controlled had definitely faded away.

Let us then recall the major episodes in the regulation of embryo use and cloning for stem cell research in the US and in Europe. This survey, however, will only sketch the regulatory landscape of stem cell research regulation, given the existence of an already copious body of literature on the topic. My aim will be that of paving the way for charting the emergence of new modes of stem cell regulation in the subsequent sections of this chapter, so as to discuss a comprehensive array of governance options in the end.

3.I.2 From self-governance to state regulation: antecedents

The emergence of new governance models to replace the social contract for science has a lot to do with debates on the use of organs for transplantation, the

protection of human subject in biomedical research, the rise of biotechnology in the Seventies, and the issue of using tissue from elective abortions. A multifarious direction of change can be observed in the way in which unsettling biomedical advancements and biotechnological progresses shaped the regulatory environment around them. I will now recall a few prominent examples from the regulatory history of the last few decades to show this trend. I will maintain that, as to the models of governance for post-social contract science, state-centred initiatives absorbed efforts on the part of the scientific community to preserve the privilege of self-regulation. The coexistence and the tension between these two models of science governance (state-centred and self-regulated) are still evident in the main regulatory events of stem cell research, as well as in the current rising of new governance options for the use of cell-based medicinal products.

Organs and death

As early attempts at using organ transplantation began in Harvard in the Sixties, an *ad hoc* committee was created at Harvard Medical School to establish acceptable criteria of donor death declaration. The Ad Hoc Committee of Harvard Medical School for Examining the Definition of Brain Death promptly issued a report that appeared on the Journal of the American Medical Association (Anon. 1968).

The paper, written by a panel mainly composed of physicians, intended to clear the way from "obsolete criteria for the definition of death [that] can lead to controversy in obtaining organs for transplantation" (Anon. 1968, 337). It thus spoke the language of scientific modernization – one that can extend its reach to bear on philosophical ideas about life and death. But the panel was also aware of the increasing cultural pressure elicited by advancing biomedicine, hence the necessity to adjust an outworn conceptual landscape to the new emerging necessities of science. The paper was a clear example of how the production of social order and that of medical knowledge reciprocally interacted

to stabilize the emergence of a new technology like organ transplantation. Most importantly to our concerns here, the report assumed that the medical doctors themselves could manage the wider cultural and societal consequences of their job, and that the appropriate audience for those reflection was the professionally coherent readership of JAMA. In the case of the Ad Hoc Harvard Committee, the wider consequences of introducing a major surgical innovation were taken care for by the very same institutional and professional groups of people that were actually attempting to develop such novelty.

If this attempt at self-regulation seems in line with the tenets of scientific independency heralded by the social contract, a crackle in the framing of the latter has nonetheless to be noticed. Allegedly for the first time, biomedicine had to provide public (albeit in a rather restricted sense) justification for its activity, as it started to exert a destabilizing cultural influence on its surroundings. This instance of scientific engagement in justificatory practices within the public sphere, signals the inadequacy of the social contract model and points to the emergence of new modalities to cope with the moral disagreements that biomedicine can provoke.

The 1968 report from the Harvard committee, however, gave rise to endless controversies over the most appropriate definition of death, to assure that explant from dying donors was undertaken under ethically acceptable circumstances. Importantly, it has to be noticed that such debate eventually resulted in *Defining Death*, the 1981 report of the *President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research* (Anon. 1981). As a matter of governance, the self-regulative model of the Harvard commission simply could not provide enough support to a practice as culturally unsettling as organ explantation. With *Defining Death* the

insufficiency of the self-regulatory model of science governance becomes apparent. In the words of the report,

> «medical criteria alone cannot meet the public concern, which arose not only because of advances that complicated the decisions of physicians, but also because the public perceived a departure from long-accepted social standards for differentiating life and death. This departure seemed to have momentous implications for many social practices and institutions» (Anon. 1981, 40:45).

As a consequence of the fact that "the definition of death can touch social life so profoundly, […] the need for law is perceived" (ibidem). The document by the presidential commission acknowledged a plurality of normative sources for the legitimation of public decisions on organ donation, including but not limited to medical authority. The commission thus conceived of a gradient of increasingly stabilizing and legitimizing sources for the governance of scientific matters that spanned from professional authority to judicial review of the Common Law to national and, eventually, federal regulation. This new model is plural in acknowledging such variety but clearly confer to the highest ranks of the legislative pyramid.

Genetic engineering

Very much around the same period of time, a similar regulatory trajectory could be seen to be at work in the case of recombinant-DNA (r-DNA). When in the early Seventies r-DNA technology became a reality, suddenly the scientific community, as well as politics and society at large, realized that something had changed in the nature of what scientists could do in the lab. Molecular biology, so far sheltered in esoteric laboratories, and thus removed from the public eyes, turned into a major site of collective imagination,

as soon as DNA, a symbolic reservoir of human identity par excellence, became amenable to previously unthinkable manipulations. As early as in 1974, a National Academy of Sciences appointed committee autonomously decided to suspend research on r-DNA until the risks connected to this technology were qualified. One year later, in the famous Asilomar conference, the scientific community gathered to discuss those risks and to devise measures to manage their containment. Asilomar framed the risk of using r-DNA mainly in terms of containment of the organisms used to perform recombination experiments. As a matter of fact however, the guidelines resulting from the Asilomar conference represent a sociologically relevant example of an emerging governance model for biotechnological research. The scientific community used Asilomar to convey an image of itself. The self-imposed moratorium and the guidelines for risk containment purportedly showed that the scientific community was able to isolate and to define the public consequences of technological development on its own. In this sense, science qualified as a competent moral partner in social co-operation, rather than an accomplished bearer of purely technical expertise. This all effort of self-regulation not only proved the confidence of the scientific community in its capacity to control the behaviour of its individual members, but also showed that science was good at sensing the wider social worries that may arise about its use, and at taking measure to meet those preoccupations (Blasimme 2011). It didn't take much however, that this self-regulative model showed inadequate to cope with the rising concerns over the use of r-DNA. In 1982, President Carter's Commission on the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, issued a report titled Splicing Life, affirming that "[t]he recent work in molecular genetics may again unseat some widely held—if only dimly perceived—views about humanity's place in nature and even about the meaning of being human, [so that] it cannot be long before the new knowledge and

new scientific powers begin to have an impact on general thinking" (President's Commission for the Study of Ethical Problems in Biomedical and Behavioral Research 1982, 17). The perception that molecular biology was likely to elicit "deep anxieties" (idem, 2) in the public, lead to the realization that public oversight was indeed missing about the wider social implication of scientific research. The Commission suggested that public organs be responsible for advising policy-makers as to the technical and ethical consequences of biotechnological innovations such as r-DNA. It is noteworthy that, already in this early phase of biotechnology, and notwithstanding the mainly scientific composition of the President's Commission, the suggestion arose that ethical analysis should have been carried out not exclusively by politicians, nor by scientists alone. To this last point, the report clearly recognizes that "[t]he careful attention paid by scientists, private groups, and government officials to the immediate health and environmental risks has been rewarded with a record of safe and fruitful research and development" (President's Commission for the Study of Ethical Problems in Biomedical and Behavioral Research 1982, 81). However it also reminds that "[t]he issues [of genetic engineering]are so wide-ranging as to require a process that is broad-based rather than primarily expert, since the issues cannot be resolved on technical grounds alone and since many of the most knowledgeable scientists are deeply involved in the field as researchers or even as entrepreneurs" (President's Commission for the Study of Ethical Problems in Biomedical and Behavioral Research 1982, 82). Ideally, an enlarged panel comprising scientists, members of professional organizations, representatives from the industry, specialists in ethics, law and religion, as well as of lay members of the citizenry should discuss issues generated by the advancement of science and biotechnology. The history of state regulation of biotechnology thus initiates with the perceived necessity to make discussion

and decision-making as accountable as possible to a wider public than to the scientific research community alone.

Foetal research

Among the issues under discussion in those times, there was also the possibility for biomedical researchers to use tissues of electively aborted foetuses to conduct scientific investigations and to attempt clinical applications. Foetal tissue had effectively been used in biomedicine to develop vaccines against polio and rubella (1950s). Furthermore, a number of diagnostic advancements were made possible by the use of foetal tissue samples including Rh incompatibility detection, amniocentesis, detection of developmental abnormalities, development of obstetrical anaesthesia and treatments for maternal conditions (Institute of Medicine 1994).

Moreover, aborted foetuses represent one possible source of stem cells to be used in medicine and research. Cell lines of foetal origin were established during the development of the polio vaccine, and their sustained proliferative potential was exploited for that purpose. Furthermore, the absence of mature surface markers on neuronal stem cells in foetal brains makes them an immunologically apt to transplantation in patients with neurodegenerative diseases.

Indeed, tissue from aborted foetuses was employed in experimental transplantation for various conditions like Di George Syndrome, Parkinson's disease, Alzheimer's disease, and spinal cord injury, but also leukaemia, aplastic anaemia, blood clotting disorders and juvenile diabetes (Coutts 2009).

These medical possibilities however intercepted the harsh debate on the legalization of abortion in the States, as well as in many other countries, and the worries elicited by the already mentioned scandals on the inhumane treatment of biomedical

research subjects. On the one hand, many commentators were worried of the possibility that, linking clinical utility to the practice of voluntary, would project a favourable light onto the practice of abortion itself. On the other hand, however, another major point of controversy in the debate on foetal tissue research was relative to the perceived disrespectful treatment of the unborn on the part of researchers performing mutilations to harvest tissue from foetuses., This line of argument often included the idea that research on foetuses, other than being morally unscrupulous per se, might be the first step towards the kind of moral perverseness of Nazi experiments (Bopp and Burtchaell 1988).

The same *National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research* that was working on what will then become the Belmont Report (1979), was thus charged to investigate also the medical and ethical prospects of foetal tissue research. In the meantime, in 1974, the Department of Health, Education and Welfare (HEW) banned public funding on foetal tissue research. The Commission held public hearings and collected opinions from scientists, philosophers and legal scholar, eventually resulting in the 1975 recommendation to lift the ban and proceed with foetal tissue research.

Analogous liberal provisions were adopted by dedicated commissions and advisory panels in many other countries outside the US (Coutts 2009, II).

Although in a climate of unsettled moral disagreement, foetal tissue research continued nonetheless, until it became again a matter of public controversy in 1987. Lured by apparently successful experiments with the transplantation of foetal neuronal tissue into the brain of two Parkinson's patients (Madrazo *et al.* 1987), NIH director James Wyngaarden sought the approval of the Department of Health and human Services (HHS)

for funding similar research at NIH. HHS decided to suspend the decision until an advisory committee could analyze the moral stakes of the proposal and issue appropriate recommendations. Again, public funding on this kind of research was stopped, whereas privately funded research project could still in principle go ahead with their studies. The commission that convened at NIH was composed of medical scientists, but also included experts in ethics, law and religion, and was called *Human Foetal Tissue Transplantation Research Panel*. The panel reported one year later that, also in accordance with similar regulatory frameworks in other countries, it found foetal tissue research morally acceptable with a majority of 18-3. This opinion notwithstanding, the freshly appointed Secretary of HHS under the Bush Administration, allowed hearings of the three dissenting members, and eventually extended the moratorium on federal funding on transplantation research using foetuses from elective abortions in November of the same year. The official justification for this decision was, again, the idea that permitting this kind of research would have resulted in increasing the number of induced abortion. It should be noticed however, that this issue, just like that of stem cell research a few years later, soon became a matter of political identification for US presidencies. With the election of President Clinton in 1992, the ban was lifted and this kind of research could resume.

With the case of foetal research, the state-centred model of scientific governance comes to maturity. It was no longer a scandal for politics to restrict science, and actually, the need to bring science into the core of the political agenda, comes to be seen as a defining demand for democracy itself. In the US, as well as in many other countries, the transition from the 'social contract for science'-model to state-centred patterns of governance, had to pass through the realization that scientific self-governance was insufficient to ease the mounting moral disagreement generated by biotechnologies. The

ways in which states go about regulating such complex matters is often characterized by nation-specific patterns of governance. Indeed however, self-governance initiatives are still possible and continue to proliferate also in this mutated scenario. The two models however remained in tension, as scientists still made up most of the advisory committees that proposed legislative initiatives, and professional associations continued to issue guidelines to govern their members' activities. In this last respect, it has to be noticed that guidelines and codes of ethical conduct have been issued by the American Academy of Paediatrics, the American Medical Association, the British Medical Association, and the Swedish Society of Medicine. The burden of public accountability nonetheless, proved difficult to bear for the scientific community alone. Politics had to provide institutional framing to the controversies caused by early stem cell medicine and research, and it thus set the stage for the regulatory infrastructure of the future.

A defining feature of this emerging scenario is worth recalling here. To the extent that biotechnology and biomedicine became a matter of national policy-making initiatives, a line of demarcation seemed to be reinforced by such legislative interventions, one that severed public form privately funded research. The examples above recall emergence of a governance model whereby the use of public moneys for innovative scientific research became a matter of political decisions. One should however recall that in the case of biotechnology, scientific and technical advancements fuelled and were made possible by an intensifying narrative of national technological supremacy that clearly saw the leading nations of the West racing to gain dominant positions. Moreover, this narrative was sustained by the hope of a wave of economic growth to be channelled through emerging biotechnologies. In this context, regulation of ethically sensible scientific matters left the private sector untouched by the political restrictions that constrained publicly sponsored research. Such dispensations were retained in stem cell

policies as well, as the boundary between publicly founded and private research remained a barrier to public regulation, with the only exception of the ban on human reproductive cloning, as noted by Gottweis and colleagues (Gottweis, Salter, and Waldby 2009, 70).

3.I.3 State regulation of stem cell research

The brief excursus of the previous sections tracked the emergence of a specific mode of governance for biotechnological and biomedical innovation. In its early phases, the governance of strongly contentious scientific matters like those elicited by technical progress in the life sciences, took the form of both state-centred initiatives and effort at expert self-governance. The latter were based on the opinion of restricted, albeit diverse panels of experts. Eventually, however, policy-making remained firmly in the hands of the political power that acted primarily through the possibility of restricting funding on morally and politically undesirable research. This model became a blueprint for the governance of stem cell research either, just a decade after, with the only difference that the advisory function, in the case of stem cell research, was performed by national bioethical commissions rather than by scientific experts sitting in dedicated panels.

Through the issue of foetal tissue research, unborn human conceptuses, already an object of fierce ethical and legal controversy in the case of abortion, acquired the status of distinctively political objects. As I have shown above, regulating this kind of research became the occasion for restructuring the whole relationship between research science, politics and medicine. This relationship, it has to be said, was also in the course of being transformed by the dynamics of industrialization that biotechnology brought into the previously isolated academic environment of science. It is therefore apparent that the

social contract for science that had been dominant since the second half of the 1940s, came to be replaced by different modalities of research governance.

The history of how regulatory novelties of the kind described above became entrenched in the governance of stem cell research after the episodes relative to foetal tissue research is a complicated one. Moreover, this history has been extensively reconstructed and reviewed in dedicated scholarly literature (Gottweis, Salter, and Waldby 2009). I will therefore only briefly recall the major events of this political trajectory with the intent to provide further support to the idea that stem cell innovation is as much a matter of scientific ingenuity as it is a matter of political transformation.

With the successful creation of Dolly the sheep in 1996, not only the idea that eukaryotic cells possess remarkable degrees of molecular plasticity was demonstrated to the scientific community. The cloned animal became the visible embodiment of a technical peak for biotechnology to the ensemble of humanity. Somatic cell nuclear transfer (SCNT) soon gave rise to widespread concerns regarding the allegedly uncontrollable leap in the technical ability of science to manipulate life. People started to see cloning as technique that appropriates life itself, thus depriving it of the sedimented meanings that humanity attaches to it. Such discourses are recurrent in the Nineteenth century narratives about science. They thus soon became part and parcel of the discursive memory (Maingueneau 1984) of stem cell science as well.

As cloning became a possibility in 1996, public calls for a ban on this technique emerged promptly. With SCNT traditional intuitions about the boundaries of life suddenly lost grounds, thus urging regulators to fill this cultural gap with political initiative. It has been noticed that Britain handled this task in the context of the already existing framework of the 1990 Human Embryology and Fertilization Act (HFEA), and that this led

the country to better accommodate the worries generated by the birth of Dolly (Gottweis, Salter, and Waldby 2009, 63). Under the aegis of the House of Commons Science and Technology Committee, the British Human Genetics Advisory Commission (HGAC) immediately started a joint working group with the HFEA. The aim of such working group was to initiate an exercise of public consultation on the issues raised by the possibility of human cloning. This collaboration resulted into *consultation document* (the 1998 'Cloning Issues in Reproduction, Science and Medicine' report) that formed the basis of the public consultation. Following this document, later the same year, a second committee was charged to respond to the challenges posed by the then brand new issue of embryonic stem cell research. The use of SCNT for research purposes thus became stabilized in British legislation in late 2000, when this second committee, chaired by Liam Donaldson, issued its report. The latter basically restated the recommendations of the HFEA-HGAC panel as to the prohibition to attempt human reproductive cloning. As to stem cells instead, it allowed HFEA to license the use of cloning techniques to derive hES cells. The British Government and Parliament ratified such suggestions and incorporated them in legislation.

In the US, a 1995 bill known as the Dickey-Wicker amendment prohibited the use of federal funding for the creation of human embryos for research purposes, as well as all research activities in which human embryos need to be destroyed. Moreover, as soon as in early 1997 – days after Nature announced the birth of Dolly via SCNT – President Clinton asked his National Bioethics Advisory Commission (NBAC) to express recommendations on human cloning. President Clinton did not even wait for the report by NBAC to be delivered and issued a moratorium on human cloning in March. Later that year, the NBAC report eventually came out, supporting a ban on human cloning that was promptly translated into the Cloning Prohibition Act. Interestingly, the latter extended to

both public and private sectors, stating that any attempt to create a child via SCNT should be considered immoral. Notwithstanding this restriction, stem cell research could be carried out in the States by using public money on pluripotent cells derived from donated IVF embryos. According to the 2000 NIH *Guidelines for Research Using Human Pluripotent Stem Cells*, and in conformity with the Dickey-Wicker Amendment, federal money could be used to work with hES cells, but not to derive them from donated embryos. Nor research could be funded with NIH money if the embryos were created via IVF with the specific aim of being used in research. In other words, NIH grants could only go to research projects that made use of pluripotent cells from IVF supernumerary embryos, provided those money were not employed in the derivation process, that is to say, to pay for a procedure that entailed the destruction of a human embryo.

The fate of this regulatory tool is known. On August the 9th 2001, in his first public address to the nation, President Bush further restricted the dispositions issued by the NIH a few months earlier. He announced that not only public money could not be used to destroy supernumerary IVF embryos for research, but also that public money should not go on research using cell lines of embryonic origin derived after the day of the announcement. Research could thus be funded by the NIH only on existing hES cell lines, but new lines could only be produced and studied with the aid of private money. Notoriously, President Obama relaxed this regulations in 2009, when he re-established the conditions set forth by the NIH in 2000.

3.I.4 Pervasive epistemologies

The model of governance described thus far enjoyed widespread application in many countries willing to join the global race of stem cell biotechnology. All emerging national actors in stem cell research adopted a state-centred regime of governability,

coupled with the advice of dedicated bioethical expertise and, at times, with open engagement in exercises of public consultation. It is worth remarking however, that the same model gave rise to different regulations in different countries, inspired by varying degrees of permissibility as to the procurement of embryonic material for stem cell research. On a gradient ranging from the possibility of both cloning and creating *ad hoc* IVF embryos for research (Belgium, India, Israel, South Korea, UK), to the prohibition of even importing hES cell lines from abroad (Austria, Ireland, Lithuania, Poland and Slovakia), different countries adopted variants of the same governance model to articulate their scientific policies.

Gottweis and colleagues have classified the different regulatory regimes according to those variants, and have convincingly argued that bioethics became "the political means for the creation of a global moral economy in which the trading and exchange of values is normalized and legitimated" (Gottweis, Salter, and Waldby 2009, chap. 6). In all such different political arrangements, bioethics attained political relevance by means of its principle-based approach to the discussion and resolution of allegedly intractable moral dilemmas raised by the advancement of modern medicine and technology.

Bioethics played thus a crucial role in the emergence of a stable global order around stem cell research. This role, it has been argued, is due to "its impartial functionality for the governance of science rather that from any localized source of historic or cultural authority such as religion" (Gottweis, Salter, and Waldby 2009, 131). The alleged substantive neutrality of bioethics, other than being acknowledged as a distinctive reason for its successful dissemination into national governance strategies, has also been a source of major criticisms. According to some commentators, this alleged neutrality put bioethicists in the position to exclude the legitimate interests of those who do not articulate their moral standpoints in the terms of the canonical principles of

bioethics. Based on the exclusive character of principled bioethics, critics have called for the sociological deconstruction of the presumed neutrality of bioethics (Hoffmaster 1994; Evans 2000; Evans 2002; Bird, Conrad, and Fremont 2000; Hedgecoe 2004).

The universalistic character of canonical bioethics, however, is contradicted by the variety of moral articulations that the bioethical discourse gave rise to in the application of the state-centred model. The language of bioethics did not constrain the directions that the moral discourse on stem cell research eventually took in individual countries. However, it provided a means for the instalment of moral reasoning into the very core of legislation. To better appreciate this function, it is useful to briefly recall that other governance options surfaced along the way of the regulatory history of stem cell research, but failed to secure the means of political stabilization.

The search for alternatives to the use of pluripotent cells of morally problematic kinds is one of such attempts. The divide between supporters of embryonic sources and those who insisted in using adult stem cells only characterized a moral as well as an epistemic battlefield. The construction of the moral acceptability or unacceptability of embryonic stem cell science, to a good extent, relied exactly on the experimental probing of the clinical usefulness of hES cells and adult stem cells respectively. But the debate on technical alternatives to embryonic cells reached major levels of ontological sophistications as researcher found technical ways to allegedly bypass the moral complications of embryo-derived cells. Single cell biopsy, for instance, is a procedure by means of which Lanza and colleagues managed to retrieve only one blastomere from the early embryo, thus leaving the latter viable and functionally integrated (Klimanskaya *et al.* 2006). Another alternative is to use embryonic artefacts as sources of pluripotent cells. One such possibility was conceived by William Hurlburt, a member of the PCB, and realised by MIT scientist Rudolf Jeanisch. The latter genetically modified the somatic

nucleus before the SCNT procedure. In this way he obtained an altered nucleus that, upon cytoplasmic reprogramming into an enucleated egg, is genetically unable to implant in a uterus – due to the lack of Cdx2, a gene that is indispensable for the early embryo to implant. The procedure was therefore dubbed Altered Nuclear Transfer, or ANT (Hurlbut 2005) Such alteration, according to the inventor of this methodology, deprives the embryo of its developmental potentiality. It thus impinges on the alleged moral status of the embryo, that so often in the debate has been attached to the potentiality argument (Testa 2009). A further technical way out from the moral controversies generated by hES cell research is the availability of induced pluripotent stem cells. The latter gave rise to a specific discussion as to the opportunity of either abandoning hES cell research in favour of iPS cells, or pursuing the two strand of research in parallel (Cyranoski 2008; Gottweis and Minger 2008; Zarzeczny *et al.* 2009; Zarzeczny; Caulfield *et al.* 2010). Most commentators agree in seeing iPS cells as a promising field of scientific investigation in its own terms. None of them, however, suggests that iPS might replace hES cells. Finally, one should also recall the already mentioned recent advances in the field of somatic cell direct conversion from one tissue type to another as a possibly interesting resources to avoid the controversial use of cells of embryonic origin.

All the above possibilities can be usefully understood as the result of what has been called responsive epistemologies (Testa 2009). This notion points to the idea that "the experimental process and the biotechnological object respond to a variety of social, ethical and legal concerns and accommodate them within their epistemological texture" (*ivi*, 1624).

Such constructions of morally and politically more tractable scientific objects, certainly represent a remarkable new feature of biotechnology. They embody the co-production of scientific and political order and aim at technically stabilizing the boundary

between the two. Such strategy has also enjoyed some form of political endorsement at least in the States, when Leon Kass' President's Council of Bioethics issued a with paper called *Alternative Sources of Human Pluripotent Stem Cells* in 2005. The report included most of the above-cited methodologies for avoiding the use of embryos. It drew inspiration from realizing that "people of all moral and political persuasions should be pleased to learn that scientists and others are creatively seeking morally unproblematic and uncontroversial ways to advance" scientific research (ref). Allegedly, responsive epistemologies are therefore a way to preserve moral pluralism while nurturing scientific progress. Whereas the law retains prescriptive prerogatives in the case of Thomson-like hES cells, it can conveniently be supplemented or replaced by biotechnological ingenuity in the case of ANT embryos or iPS cells. In this respect, Testa correctly interprets the silencing of Cdx2 in ANT embryos as the sign that "in the age of biotechnological kind making, genetic engineering becomes, alongside the law, a significant tool for social ordering" (Testa 2011, 98).

As a matter of fact however, looking for technical alternatives to proper embryo-derived stem cells proved short-sighted for at least two reasons. First, it is true that pluripotency is a multiply realizable cellular state, but not all pluripotent cells look equal in terms of the genetic and epigenetic profiles. Therefore, even if science might one day resort to one derivation method and discard all the others, it remains indispensable, at the very least for reasons of comparability, for scientists to keep on working on the better characterized kinds of pluripotent cells, that is to say, hES cells. Second, all the supposed alternatives to the use of the latter, albeit morally more friendly than their embryonic counterpart, retain most of the problems implied by egg donation, informed consent, privacy, clinical safety and utility. This is why responsive epistemologies did not quite

establish themselves as a politically reliable alternative to the state-centred governance model.

The inability of responsive epistemologies to establish a scientifically credible and socially robust alternative to state-centred initiatives is yet another demonstration that the latter provided a better platform for plausible regulatory frameworks to emerge. In this context bioethics proved integral and functional to the formation of a discursive sphere of support for policy-making. Indeed, in the vast majority of the countries where national ethics committees were involved in consultation over stem cell research, public debate also happened to take place (source Gottweis, Salter, and Waldby 2009, 139). This was crucial to the instalment of state-centred modes of governance for stem cell research. States however sought public support not so much on the ethics of stem cell research but on the importance of this field of science as a driver of economic growth. Scholars have framed this aspect of scientific governance as driven by the effort of 'competition' states (Cerny, 1990, 1997; Hay, 2004; Hirsch, 1991) to gain or maintain hegemonic positions in the global economy of biomedical innovation (Salter and Salter 2010). In this sense also governance manoeuvres that apparently restrained scientific freedom to do research on embryonic material – like the Dickey-Wicker Amendment and the August 9 2001 Bush further limitations on federal funding – ultimately left ample room for private investors and individual state funding in the US. State-centred modes of governance are thus understandable as integral to national strategies to maintain or expand the competitive edge in the global race of biotechnology. States that wanted to compete for hegemonic positions in the speculative market of stem cell application, however, did not only have to provide favourable regulatory conditions for embryonic stem cell research. Moreover they had to pay special attention to the cultural consequences of stem cell science so that acceptable levels of public support back up this

scientific enterprise. The compromise solutions of the US, or the tightly overseen licensing system of the UK can thus be read as efforts in the direction of stabilising the societal attitudes towards research with pluripotent material.

Chapter 3 - Part II: An emerging shared regulatory model for the governance of stem cell clinical translation

In this chapter I will reconstruct the emerging new governance regime of stem cell clinical innovation. I will start by considering the multiplicity of regulatory tools that emerged to exert control on the development of stem cell clinical development (3.II.1). I will then analyse the features of what a call a shared model of governance (3.II.2). Subsequently, I will assess this model from a political standpoint in the light of a deliberative account of politics (3.II.3)

3.II.1 Multiple regulatory dispensations

In this section I will show how the regulatory regime of embryonic stem cell research stem cell has changed in the case of *translational* stem cell research.

A body of documents and regulatory tools is growing that addresses concerns of clinical safety and medical utility of stem cell-based products and devices. To mention but the most important ones in the US and Europe, one should at least recall what follows.

The FDA started drafting new regulation on cell products as early as in 1997, in the context of the sixth "Reinventing Government" initiative. In the report that summarizes the vision of the initiative, measures started to be conceived to reduce the incidence of communicable disease infection, and contaminations during the handling and clinical use of human tissue. As stem cell science grew, similar recommendations were systematically applied in dedicated regulatory dispositions, including:

- Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (8/8/2007)

- Guidance for FDA Reviewers and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy Investigational New Drug Applications (INDs) (4/9/2008)

- Guidance for Industry: Considerations for Allogeneic Pancreatic Islet Cell Products (September 2009)

- Draft Guidance for Industry: Current Good Tissue Practice (CGTP) and Additional Requirements for Manufacturers of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) (1/16/2009)

- Final Guidance for Industry: Potency Tests for Cellular and Gene Therapy Products
  (January 2011)

From a general standpoint, in assessing applications for clinical trials, FDA assimilates stem cell therapies to existing somatic cellular therapies.

This is testified by the fact that, in order to initiate a stem cell-based clinical trial, an applicant has to file a request for an Investigational New Drug (IND) in the field of biologics[6]. As a consequence, stem cell clinical research is taken not to require any further

[6] Biologics are all those medicinal products that are not created through chemical synthesis but via biological processes. They include: vaccines, blood and its individual components, antibodies, cells, bodily tissue, recombinant proteins and genes for gene therapy.

regulatory oversight than other, more traditional, cellular products and therapies like, for instance, bone marrow transplantation.

Therefore, the traceability of cellular products, and adherence to good manufacturing practices in their handling are required for stem cells as for any other biological material used in clinical research. In particular, very much like other tissues, also the use of stem cells has to obtain clearance from the original tissue/embryo donors, and must take measures to assure the absence of infectious or genetic diseases in the cells to be used *in vivo*.

As to the use of stem cells in medical practice, they are regulated in the same way as other biological products, that is, with the only aim of preventing disease transmission from donors to receivers – under Section 361 of the Public Health Service Act, provided that the cell product: is only minimally manipulated (i.e. not cultured *in vitro* after retrieval), and is intended for autologous use only (Code of Federal Regulations – CFR – Title 21, Section 1271.10). This means that, for instance, clinics can provide unproven stem cell treatments only if the above criteria hold. Therefore, at least in the States, it is not forbidden to extract cells from a patient and re-inject them into the same patient. The medical significance of such procedure is highly questionable and, to date, the efficacy of such practices remains unproven. However, a number of clinics are offering this kind of "treatment" on the market, thus raising debates and litigations that I will account for in the next chapter.

It has furthermore to be emphasised that FDA, other than using a dedicated division for overseeing stem cell research (the Cell Therapy Branch of the Centre for Biologics Evaluation and Research), avails itself of two dedicated bodies to deal with stem cell clinical research. One is the *Human Tissue Task Force* (HTTF), created to evaluate if

cell therapy demands further specific measures on the part of the Agency to protect public health. The Task Force is made up of FDA officials belonging to the Centre for Biologics Evaluation and Research (CBER), the Office of Regulatory Affairs (ORA), and the Office of the Commissioner (OC). The other is the *Cellular, Tissue and Gene Therapies Advisory Committee* – a commission of 13 "authorities knowledgeable in the fields of cellular therapies, tissue transplantation, gene transfer therapies and xenotransplantation including biostatistics, bioethics, hematology/oncology, human tissues and transplantation, reproductive medicine, general medicine and various medical specialties including surgery and oncology, immunology, virology, molecular biology, cell biology, developmental biology, tumor biology, biochemistry, rDNA technology, nuclear medicine, gene therapy, infectious diseases, and cellular kinetics" (source: www.FDA.gov). The aim of this body is to review and evaluate "the safety, effectiveness, and appropriate use of human cells, human tissues, gene transfer therapies and xenotransplantation products which are intended for transplantation, implantation, infusion and transfer in the prevention and treatment of a broad spectrum of human diseases and in the reconstruction, repair or replacement of tissues for various conditions" (*ibidem*).

The regulatory attitude of the FDA is a clear attempt at normalizing the clinical development of stem cell science, but it does not deny the very specific and ethically sensible features of stem cell translation. In particular, the FDA is aware of the fact that the peculiar biological characteristics of stem cell products have an impact on the safety and efficacy evaluation of the relative clinical trials. To begin with, self-renewal and pluripotency may indeed result in the formation of teratoma in clinical research subjects. What is particularly dangerous about this kind of event is the possibility of teratoma occurring at sensible sites such as the brain or the heart of the patient. Furthermore, stem cells and derivatives, due to protracted *in vitro* culture, might have developed

alterations (genetic, epigenetic or chromosomal) that may lead to malignant transformation *in vivo*. A further possibility is that induced pluripotent stem cells and derivatives, if created by viral transduction, may suffer from dangerous mutagenic insertions caused by the viral vectors, thus resulting in potentially tumorigenic and uncontrollable behaviours *in vivo*. With respect to such dangers, the FDA requires extensive characterization of stem cell products, as well as sustained refinement and improvement of multiple testing strategies that range from morphological analyses, to specific biomarkers detection, and genomic and proteomic evaluations. This is why FDA, by means of the scientific expertise it gathers and distributes into specific advisory bodies, seeks a continued dialogue with applicants to prevent adverse events or, ultimately, cope with their occurrence.

However, preventing dangerous cellular material form ending up in clinical research subjects also entails the development of better purification protocols and cellular sorting techniques, together with improved animal model organisms and preclinical study designs to yield more robust proof-of-concept evidence before starting clinical trials.

Normalization efforts thus encounter a limit in the technical specificities of stem cell products. Most of the ethically sensible stakes of stem cell translation, such as improving safety through cellular purity and genetic integrity, depend on the future development of more accurate tools to reliably analyse cellular products. As a consequence, it is currently difficult for regulators to set tight standards and enforceable dispositions. In other words, the still evolving state-of-the-art of cellular manipulation, does not make it feasible for regulatory agencies to implement precise norms that efficiently cope with all the potential risks of stem cell translation to human subjects.

California, being a major player in the global race to stem cell clinical innovation, has also issued dedicated regulations to govern this kind of research. The California Institute for Regenerative Medicine (CIRM) Medical and Ethical Standards Regulations (February 3rd 2010) establish that a dedicated Stem Cell Research Oversight Committee (SCRO) must review and approve any CIRM-funded attempt to introduce cells from covered stem cell lines into live born humans. Similarly, the California Department of Public Health (CDPH) Guidelines for Human Stem Cell Research – issued by the Human Stem Cell Research Advisory Committee – sets out review and approval functions of a national SCRO committee to evaluate research outside CIRM. This document declares that the competence of the SCRO members shall include developmental biology, stem cell research, molecular biology, assisted reproduction, as well as expertise in the ethical issues of stem cell research. Moreover, the SCRO panel shall include at least a non-scientists member of the public and at least one patient advocate.

At the European level, similar authorities were installed at the European Medicines Agency (EMA), although they are not dedicated to tissue and cellular therapy specifically. On the one hand, the *Innovation Task Force* (ITF) is a multidisciplinary commission comprising experts in regulatory, legal and scientific issues, and providing agency-wide coordination as well as early engagement with EMA applicants. Furthermore a *Scientific Advice Working Party* functions as a specific body providing dedicated technical assistance to companies that are in the course of developing new human medicines. Of relevance to the development of stem cell medicine, is the establishment within EMA of a Committee for Advanced Therapy (as mandated by Regulation EC No.

1394/2007) charged, among other things, of evaluating advanced therapy medicinal products in marketing authorization procedures. Moreover, EMA issued documentation concerning the possible clinical use of cellular products, including among others:

- the "Guidelines on Human Cell-Based Medicinal Products" (11th January 2007);
- a "Reflection Paper on Stem Cell-based Medicinal Products" (6th March 2007);
- the "Final Report from the EMA/CHMP-think-tank Group on Innovative Drug Development" (22nd March 2007);
- and the "Guidelines on Strategies to Identify and Mitigate Risks for First-in-human Clinical Trials with Investigational Medicinal Products" (19th July 2007).

The European Group on Ethics in Science and New Technologies (EGE) had also released a report on the "Ethical Aspects of Human Stem Cell Research and Use" in 2000 that gives some attention to issues of clinical translation. However, the most important pieces of legislation on those matters in Europe are:

- Directive 2004/23/EC of the European Parliament and the Council (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.

- Regulation (EC) No 1394/2007 of the European Parliament and of the Council on advanced therapy[7] medicinal products (November 13th 2007), amending the 2001 Directive 2001/83/EC and Regulation (EC) 726/2004 relating to medicinal products for human use.

Directive 2004/23/EC addresses the quality and safety of human tissues and cells *per se*, before they are implanted in human subjects. Its main aim is to prevent the transmission of infectious and genetic diseases from donor to receiver, and to assure that products of non-human origin, that may have been used to derive the transplanting material, do not reach the receiver. To this aims, the directive also mandates the creation of a system to assure the traceability of tissue and cells. Furthermore it restates that donation of bodily tissue should remain voluntary, unpaid, and anonymous and inspired by principles of altruism and solidarity. Interestingly, the directive also suggests information and awareness campaigns to stimulate the practice of donating to medicine and research. To the extent that this directive seeks standardization, it so does in view of the objective of reassuring the public that human tissues and cells produced in different Member States possess even high-level quality characteristics throughout. There is therefore an idea of a shared supranational biomedical community at the roots of such regulatory effort. Such community has to overcome diffidence to allow human tissue to reliably circulate within its boarders, and thus for European biotechnology to properly work.

[7] For 'advanced therapy medicinal products', the Regulation intends: gene therapy, somatic cell and engineered tissue products (Chapter 1, Article 2.1.(a)).

Regulation (EC) No 1394/2007, on its part, is an amendment to pre-existing provisions on medicinal products authorization in Europe. Its scope is to anchor gene therapy, somatic cell therapy and engineered tissue (thereafter called “advanced therapies” in the EU regulatory documents) to the rest of the European regulation on medicinal products and devices. Furthermore, the mandated creation of a Committee for Advanced Therapies within the EMA (Title 10), goes in the direction of both acknowledging the novelty represented by advanced medicine, and of normalising its presence within the accepted boundaries of biomedical innovation – an aim that is common to both these pieces of European regulation.

The UK certainly possesses the most advanced institutional design to account for innovative cell therapy. The British model originates from coordinated activity between the Human Fertilization and Embryology Authority (HFEA), the Human Tissue Authority (HTA), the Medicines and Healthcare products Regulatory Agency (MHAR), the Gene Transfer Advisory Committee (GTAC), and the UK Stem Cell Bank (UKSCB). These bodies all participate in a concerted regulatory framework that is summarized into the so-called UK Stem Cell Toolkit, a streamlined pipeline of clinical development for cellular products that may have embryonic or somatic origin, and may or may not harbour genetic modifications. Adherence to such regulatory framework is not enforced by the law, but is a mandatory requirement of the above agencies for licensing stem cell research, at both laboratory and clinical level. Interestingly, the UK Stem Cell Bank code of practice insists on the fact that standards, albeit voluntary, i.e. not imposed by a law, are set forth in the interest of scientists themselves who are described as having “a desire for there to be ethical oversight of all work involving human embryonic stem cells” (page 2). In the intentions of the British regulatory apparatus, the entire framework “should provide

confidence and reassurance to professionals and the public alike that stem cell research in the UK is performed to best practice and is conducted within a transparent and ethical framework"[8] (page 6). Again, it is possible to see here an effort by the British regulators to normalize the translation of stem cell research into the clinical context by inserting this activity into a credible framework of procedures handled within reliable and trusted institutions and authorities. It is worth mentioning that such normalisation effort endorses a peculiar view of the circulation of human cellular material for research and clinical applications as well. Namely, the inspiration backing the British regulatory framework upholds what has been understood as an open source model (Courtney *et al.* 2011) entrusted and enacted directly by the UK Stem Cell Bank. This institution is affiliated with the Medical Research Counclil (MRC) and governed by a steering committee that comprises eminent scientists of obvious academic reputation. UKSCB encourages stem cell research groups in Britain and from overseas to deposit samples of the human cell lines they use. The bank harvests cell lines from various different countries, especially of embryonic origin, but by no means limited to that type. The bank thus provides certification as to compliance of the received cells with EU/UK-level GMPs through its own HTA-approved laboratories located within the storage site itself. Once accepted by the bank, cellular samples can receive two types of certification, according to the result of UKSCB in-house testing, as either 'research grade' or 'clinical grade' human cell lines. Only the latter can then be circulated for the purpose of clinical research with human subject. Nonetheless, both research grade and clinical grade deposited stem cells are available for research groups to borrow and work with – whence the name "open source model". In this way, UKSCB seeks to gain a prominent position as a hub for stem cell circulation in the coming phase of stem cell-based regenerative medicine. The benefit

[8] This statement in particular is referred to compliance with the UK Stem Cell Bank Code of Practice.

for cell users is to obtain certified stem cells, whose biological properties are tested as to genetic stability, absence of contamination and ethical origin of the line. The latter indication means that the cells were retrieved from fully informed consenting human donors, irrespective of their biological origin – embryonic or otherwise. The intended benefit for the field of stem cell research lies instead in the amount of biological standardisation that a state-level cell banking system is purportedly able to confer to stem cell studies all over the world. The open source model is thus an attempt at reducing the amount of biological variability in the circulating stock of pluripotent entities that populate research and clinical studies. In this last respect, the open source model is also a way of coping with the mounting complexity and uncertainties that afflict the development of the technological platform of stem cells towards clinical innovation.

The first clinical grade approvals are reported to be on their way in 2011 (Department of Business Innovation & Skills, 2011). Opting for the open source model, the British regulatory system assumes technical standards of good manufacture as a reliable pedigree for human cells, both in scientific and in societal terms. From the scientific point of view, the UKSCB guarantees that deposited cells can reliably be used in research. Furthermore, from the societal point of view, the centralised quality control of the UKSCB also serves the aim of reassuring the public that all due measures are taken to prevent “un-safe” cells to reach human subjects in clinical research.

This model clearly attempts at importing the virtues of open source modes of sharing, such as openness, collaboration and a certain degree of resistance to the capture of science by industry’s commercial interests. The scientific certification of manufacturing standards, at the same time, projects technical liability on the storing-sharing activity of the bank. In broad terms, however, this framing of the problem of cell line circulation is entirely dependent on technical-scientific certification. It is ultimately technical

manufacturing standards that confer credibility and convey respectability to the enterprise of scientific research done with UKSCB-deposited cells – a feature that, as I said above, also other regulatory apparatuses like those created in the States and by European authorities happen to share with the British model. I will return on the open source model later on in the next chapter when I will discuss how this framing plays out with the actual expectations of clinical researchers and their commercial partners.

As to scientific societies, two notable such bodies have issued guidelines for the regulation of stem cells research. The National Academies of Science (NAS) have crafted their Guidelines for Human Embryonic Stem Cell Research in 2005 through a dedicated Embryonic Stem Cell Research Oversight (ESCRO) committee – composed of both scientists and, to a lesser extent, legal and ethical experts. Such guidelines have been amended three times, in 2007, 2008 and 2010. Such documents, however, other than recommending the creation of dedicated stem cell research institutional oversight committees, mainly have to do with issues of hES cell derivation, and say very little about clinical translation.

A more specific self-regulatory effort was made in 2008 by the International Society for Stem Cell Research (ISSCR). The ISSCR Guidelines for the Clinical Translation of Stem Cells comprise forty recommendations designed by a task force of scientists and bioethicists, addressing a rather exhaustive set of issues in the clinical translation of cellular therapy.

Starting form the realisation that stem cell-based medicine may be on the verge of adding innovative applications to those already available with hematopoietic stem cells, these guidelines provide advice as to how to conduct technically and ethically sound stem cell clinical research. At first, the document establishes a clear-cut distinction between responsible clinical translation – assured by voluntary adherence to the guidelines recommendations – and unproven commercial stem cell interventions. The latter, generally marketed directly to patients, are said to be a possible source of fraud and exploitation, since they are not backed by any "credible scientific rationale, transparency, oversight, or patient protection" (ISSCR, 2008, 4). I will say much more on this topic in the next chapter.

Among the most notable recommendations of the guidelines it is worth recalling here the following:

- The amount and force of regulation should be proportional to the risk involved in a given case of translational research (rec. 8);

- Genetically modified cell products have to be regulated as both gene therapy and cell therapy products (rec.10);

- Sufficient pre-clinical evidence must support the decision to start a stem cell clinical trial (rec. 11);

- Some risks are typical of this innovative field of clinical research (namely, cell proliferation and/or tumour development, exposure to animal source materials and risk connected to viral vectors), and other risks can currently be unknown, so that special attention must be paid in avoiding therapeutic misconception (rec. 20);

- If the clinical trial is addressing a condition for which therapeutic strategies of some efficacy already exist, burdens to the research subject should be minimal, and perspective advantages tangible (rec. 25);

- The efficacy of the new stem cell therapy must be assessed against the best medical therapy available for the local population (rec. 26);

- Stem cell clinical interventions are possible outside of the formal route of an EBM clinical trials only under exceptional circumstances, and provided that a number of conditions hold, including among others: those interventions are confined to a very small number of patients; there is a peer-reviewed written plan for the procedure; measures are put in place to cope with adverse events; voluntary informed consent is obtained by fully patients who are fully aware of the risk and benefits of the procedure (rec. 34);

- Regulators should explicitly seek for open discussion on the ethical issues surrounding stem cell trials and public engagement in policy making at governmental agencies (rec. 35, 37).

Those guidelines are firmly rooted in the traditions of the ethical principles and epistemic values that inform evidence based medicine (EMB) and controlled clinical trials (CCTs). Most notably, ISSCR guidance vigorously subscribes to the idea that certified scientific knowledge cannot be obtained but through the cherished procedure of peer-reviewing. This principle stands as a defining pillar in the edifice set up by the guidelines, and is referred to nearly fifteen times in the nineteen pages that make up the document. Nonetheless, ISSCR also try to make room for some minor adaptations to the paradigm of peer-reviewed clinical science by affirming the special character, and thus the need for

special oversight, for first-in-human stem cell research. Most importantly, the ISSCR guidelines acknowledge a role of regulatory oversight to governmental agencies, like the FDA in the US, thus coupling the activity of the scientific society with the authority of the state body. Both ISSCR and FDA, as a matter of fact, share similar commitments towards peer-reviewed science and ethical treatment of research subjects.

This last features, as we will see in much detail in the next chapter, clearly separates ISSCR guideline from a slightly later body of guidance documents issued by the International Cellular Medicine Society (ICMS), and currently in the course of being adopted by its members. The latter society was founded by Dr. Christopher Centeno, owner of the Regenerative Sciences clinics, that offers autologous adult stem cell treatments both in the States and off-shore. ICMS is a non-profit international organisation that brings together physicians, researcher and patient with a shared interest in innovative autologous stem cell therapies. Since, as I said, the activity of Dr. Centeno and the regulatory efforts of ICMS will be the focus of next chapter, I will not enter here into further detatils. For the time being, it is sufficient to state here that the ICMS guidelines enact a completely different model of translational research with respect to ISSCR.

3.II.2 Towards a new regulatory order

All the regulatory dispensations that I outlined above, seem to depart from the state-centred model of stem cell research governance (see chapter 3, part I) quite substantially. To begin with, the incidence of enforceable legal provisions appears to be much less prominent in the case of regulations aimed at bringing normative order around stem cell translational research. The only legally binding dispositions in the previous

section are the rather general European directives on quality standards for human tissues and cells to be used in clinical research and therapy (Directive 2004/23/EC). The rest of what I presented above comprises voluntary codes of practice, guidelines, recommendations and opinion reports that supposedly should ensure that stem cell clinical research and cellular therapy are developed under the licence of regulatory bodies and implemented in an ethically sensible way.

Beyond specific ethical provisions regarding consent, anonymity, privacy, traceability and responsible medical conduct, it seems that stem cell translation resorts to the already existing overarching ethical framework of research subjects' protection. It is indeed evident from the guidance documents that both in Europe and in the US the ethical requirements of the Helsinki Declaration, the Belmont Report, the Oviedo Convention, and the Charter of Fundamental Rights of the European Union are explicitly or implicitly considered as a solid and socially credible foundation of stem cell innovative research.

The state-centred model seems no longer worth of consideration by the stakeholders of translational stem cell research. Rather, the governance model that is emerging veers towards self-regulation by the scientific community, with the functional intermediation of highly specialized regulatory bodies. The latter, both in the States and in Europe, provide strict criteria as to the manufacture of cellular products, with respect to contamination, communicable diseases and genetic alteration (good manufacturing practices –GMPs). However, beyond these provisions, regulators tend to refrain from elaborating specific public disposition as to the possible technical and ethical stakes of individual translational projects. The legislator, in other words, constructs the scope of its intervention in the clinical translation of stem cell research as limited to GMP-related issues and informed consent, and does so by assimilating stem cells to other medical

products. This classificatory move thus extends existing regulatory authority on a novel biomedical product – stem cells. It is thus by enacting a co-productive exercise in boundary construction that regulators in both the US and Europe define stem cells as biological drugs or assimilate them to other kinds of cellular therapies that already belong to the medical standard-of-care. This exercise normalises the novelty of stem cell medicine while, at the very same time, constructing the authority of the state on the clinical translation of stem cell research. Such authority, however, is not nearly as solitary as the one exercised by public regulation in the case of stem cell derivation from embryonic and foetal materials. The rigid public governance model that had been put in place to control the highly divisive stakes of working with embryos and foetuses is no longer there for regulating the clinical translation of stem cells. In its place we now see a model of shared governance, whereby the state demands adherence to quality and informed consent standards but ultimately leaves huge margins for scientific actors, both in universities and industries, to proceed with clinical translation according to self-established criteria. Some form of oversight is certainly assured by technical offices within regulatory bodies, but those offices are ultimately composed of scientists themselves, and are not equipped with specific provisions as to the scientific and ethical assessment of highly innovative clinical research. Therefore, it is almost entirely within the scientific community that the stakes, both ethical and technical, of clinical translation are dealt with. Statutory agencies do not provide but a loose framework to construct stem cell translation as a publicly credible, safe and reliable practice. Regulatory provisions issued by public authorities primarily attain this function by framing stem cells as biological drugs, and stem cell therapy as comparable to other forms of tissue-based medicine. Both in Europe and in the US, public regulation has been oriented to a framing effort aimed at bringing stem cells under the authority of dedicated agencies. But the scope of this

authority, its effective powers, do not span as far as to dictate specific epistemic criteria of pre-clinical evidence, proof-of-concept validity, or acceptable risk in first-in-human clinical research. The latter criteria, evidently, cannot be established in advance, irrespective of the highly specific characteristics of the clinical trial or medical procedure that attempts to use stem cells in human subjects – in most cases likely for the first time. As a matter of fact, the only possibility for public regulators to exert control over the emerging field of stem cell translational medicine is to frame the field in such a way that regulatory competence can be projected onto it. To this aim, existing standards of GMP and informed consent are extended to this novel field of biomedical innovation. However, as to issues of sufficient pre-clinical evidence, efficacy and human safety, governance is left to scientific experts and interested practitioners.

The result of the dispositions illustrated in the previous section is therefore a rather unstructured, but yet precisely framed *shared* model of governance. This may be immediately explained by the fact that stem cell derivation issues are dealt with elsewhere, and that the remaining moral issues, albeit important in themselves and, I would say, crucial to the future of the field, appear as yet less divisive than those regarding the moral status of human embryos. Moreover, as I said, some of the most decisive uncertainties that lay ahead of the delivery of safe clinical research in this field, depend on as yet unavailable technical progresses in cellular characterization, purification and sorting, and thus cannot be sensibly dealt with by however alerted legislation. As a consequence, states align their regulatory powers to those of the scientific community, in a shared effort to gain control on the emerging field of stem cell translational medicine.

The emergence of such a model, however, could be seen as an effort to put in place a markedly technocratic governance model. As the medical-scientific community uses its epistemic authority and its social credibility to pave the way for the governance of

stem cell translation, bioethics is providing both the ethical expertise and the persuading accountability that a process like steering biomedical innovation requires. The presence of ethical and legal experts is nowadays entrenched in the composition of advisory panels and regulatory committees – a feature that echoes the worries and conflicts over using r-DNA technologies in the early Eighties (see *supra*). Furthermore, the recognition that the governance of such technologically advanced applications should be transparent and inclusive is, at least in principle, widespread in both the scientific community and regulatory agencies. This is apparent in the emphasis that many documents put on reporting procedures, periodic inspections, and compliance with clearly stated codes of conducts and manufacturing practices. Moreover, the necessity of including non-scientific actors (e.g. bioethicists as well as patients advocates or unspecified members of the public) in the on-going construction of a solid governance infrastructure is stressed across the board. The necessity to enlarge the panel of recognized stakeholders well beyond the scientific community is evident in the ISSCR, CDPH and NAS guidelines, as well as in the European Regulation 1394/2007 (paragraph 11 and art. 21.d), and in the British oversight system as well. One may want to question, nonetheless, whether the degree of openness and inclusivity permitted within a shared regulatory model like the one I am describing is adequate to the necessities of stem cell innovation. This question will be addressed in the next chapter, when I will characterize in much detail the emerging relationship between scientists and patients in the current stage of stem cell clinical translation. In the context of discussing unproven stem cell treatments and the complex dynamics that the latter enact, I will also say something more about how the scientific framing of clinical risk fares with the self-regulatory governance model that I thus far illustrated.

A last but distinctive feature of this shared governance model is the reliance on a stepwise conception of the clinical discovery process. As noted by Sugarman, the ISSCR

guidelines, but the same could be said of all the other dispositions that I mentioned in the previous section, "largely assume a stepwise process involving science progressing from *in vitro* research, to *in vivo* research with non-human animals, to first in human trials, to larger scale clinical trials" (Sugarman 2010, 252). Where other possibilities are considered, like for example medical innovation taking place outside a formal clinical trial process, they are taken to be exceptions dictated by peculiar clinical circumstances (See ISSCR, 2008, rec. 34). This classical outlook of the pipeline of clinical development, responds to both epistemic and political reasons. As it will become clearer in the next chapter, good scientific reasons support the field's preference for the methods of evidence-based medicine (EBM) in the development of stem cell innovative therapies. Nonetheless, the necessity to maintain steering capacities and authority over the construction of the new stem cell medicine also motivates this choice by regulatory bodies and scientific societies alike. The latter, as I will show, are indeed proactively engaged in fencing off the field from the intrusion of stem cell clinics offering unproven treatments over the counter of a rising global bio-market in innovative medical technologies.

That innovation governance was steering towards self-regulation recently began to appear also in fields other than stem cell research. When the Human Genome Project (HGP) was set up and endowed with federal funding, part of the money went for covering the ethical, legal and social implications (ELSI) of the sequencing of the human genome (Ramsay 2001). Research programmes were thus set up that tried to discuss the wider impact of such new technological achievement. Academic specialists inside and outside the life sciences were thus involved in this meritorious exercise of anticipatory analysis. Cognate branches of the academy were co-opted to discuss the technological impacts of the HGP, with bioethics playing a prominent disciplinary role. It has however been

noticed that such approach to technology assessment, albeit capable of sensing the emergence of possible conflicts and disagreements, as it was conceived, was incapable of having any effect on the course of technological development (Macnaghten, Kearnes, and Wynne 2005). The latter was assumed as a given, and the ELSI assessment process focused on its impact only, rather than on its responsiveness to perceived needs and concerns by wider sectors of stakeholders. In the last chapter, I will discuss ways of assessing technological development that, drawing on deliberative and participatory approaches of technological appraisal, are gaining prominence as usable tools to shape the course of innovation.

3.II.3 Deliberative innovation

We have now reached the point where it is appropriate to attempt an assessment of the emerging governance model for stem cell clinical translation from the deliberative point of view.

The literature on the political debate that surrounds stem cell research has focused on the State-centred governance initiatives to accommodate the use of embryonic material. Comparative analyses described how political power constrained and regulated the derivation of pluripotent cells from human embryos in different countries (Jasanoff 2005; Gottweis, Salter and Waldby 2009).

However, once those new political dispensations were put in place for embryo-related research, the focus of the debate began to slide towards the possibilities offered by stem cell therapy and, thus, issues of clinical research progressively gained prominence. This phenomenon resulted in the rising of a specific governance model to regulate stem cells' application to the clinic. As I have shown, such model, which is still in

the course of being fully developed, has to cope with the intricate admixture of technical and ethical problems that is typical of innovative therapies.

It thus appeared from my previous analyses that stem cell translation is being constructed as a regulatory matter that advisory panels within governmental agencies can handle by including scientific experts and bioethicists alike.

The incipient regulatory regimes of stem cell medicine make the case for this field of biomedical innovation to be characterised as a technological platform (see *supra*). As I hinted to above, such notion captures the fluid configuration of the innovation trajectory that is typical of stem cell medicine. In particular, the regulatory model that I described so far, reflects the technical and medical uncertainties of the field at the institutional level. Stem cell medicine is thus a technological platform precisely because the end-point of stem cell-driven innovation is unknown.

Now, our journey into the regulation of stem cell biomedical novelties testifies that governance initiatives around stem cell innovation take the developmental uncertainty associated with contemporary biomedicine at face value. Resorting to the somehow mixed expertise of dedicated advisory panels in regulatory agencies and in scientific societies, regulators admit of this open-ended character of stem cell medicine. Expertise is thus both recruited and created *ad hoc* within these teams to grapple with the unpredictable direction of clinical research.

Furthermore, an expanding array of actors is arranging around the stem cell platform. We see politicians, judges, scientists of diverse backgrounds, bioethicists, patient's groups and commercial subjects negotiating their respective roles and building a regulatory regime of innovation around a rather elusive biological entity like the stem cell (Callon 1999). As rightly pointed out by Faulkner with respect to tissue engineering, also

stem cell medicine is not adequately depicted as a technology 'sector' defined by a specific product type (Faulkner 2009). Actors engaged in the construction of the stem cell regulatory order include non-human elements as well as identifiable individuals (Latour 2005). The governance of stem cell research and clinical translation is thus made also, and to a remarkable extent, of material constraints implemented in regulatory documents, judicial dispositions, ethical codes, and technical guidelines. Interestingly, this body of impersonal but tangible bottlenecks, ultimately shape the innovation trajectory of stem cell science.

We saw stem cell-based medical products being legislatively associated with other pre-existing entities (knock-in modified genes, organs, blood) to allow for their circulation and governance. We saw advisory panels using already available bioethical frameworks to gain traction on the moral questions raised by stem cell clinical research. And finally, we saw the regulatory order being delegated to dedicated experts at the operational level.

According to the account of deliberative democracy that I provided in the first chapter, certain features should characterize the debate on policy issues of public interest. To begin with, in order for the debate on stem cell clinical research to exhibit some minimal requisites of a deliberative configuration, involved actors must offer *reasons* in favour of the policy options they propose. This first requirement addresses the possible representative advantages enjoyed by actors in dominant power relations. The fact that language is conceived in deliberative theories as the universal medium of political engagement, makes reasoned arguments the privileged means for levelling-out existing power positions, as well as a civic resource to rationalise public decisions taken under conditions of scientific uncertainty and moral disagreement.

A second crucial requirement of deliberative legitimation is *publicity*. The reasons that support public policy have to be openly spelled out. This is evidently a pre-requisite for an open deliberation to effectively take place. Publicity, furthermore, stimulates the emergence of counter-narratives and contestations even after a given policy has been approved to constitute a binding provision.

This last points introduces us to a further general requisite of deliberation, that is, openness to revision. Policies, especially in a field of rampant innovation like biomedicine, must remain open to accommodate scientific and technological novelties as possible drivers of changed ethical priorities and alternative political necessities.

Lastly, as to the language of the public dialogue in a deliberative context, attention should be paid to avoiding framing one's ideas in misleading and manipulative terms. This unfortunately occurs quite often in ethically charged public debates, when holders of opposing views address each-other willingly misrepresenting the ideas of the other party, or attributing to their own positions virtues and advantages that are either not unique to them or unjustified.

Deliberative virtues, in other words, require a universal commitment to use fairness and veridicity in linguistic exchange, and this starts from respecting the value of circulating views even if one disagrees with them.

To this point, for instance, in analysing recent developments in embryonic stem cell policy in the States, Dresser has highlighted that President Obama's intervention to lift previous restrictions, "cautioned against exaggerating the possibility of medical benefits for [stem cell] research" (Dresser 2010, 339). Furthermore, the views of those who, contrary to the ideas of the Obama administration, oppose embryonic stem cell research were not depicted as merely irrational and misplaced. Rather, although

regulation was unfavourable to them, they were acknowledged as legitimate and animated by sincere moral concerns (*ibidem*).

If we now apply the deliberative criteria to the state-centred and the shared model in a comparative fashion, we will appreciate that, for different reasons, none of the models is fully satisfactory. Nonetheless, as to the latter, it seems friendly to deliberative ideals and amenable to interesting improvements.

The shared model seems better equipped to provide reasoned argument in justification of policy choices than the state-centred one. In the end, scientists are culturally accustomed to exchange reasons, and the peer-review model of knowledge certification that sometimes appears in current regulations and guidelines is an instance of such tendency. Moreover, knowledge-producing communities cannot but adopt and exploit shared technical languages, and this predisposes their members to consider each voice, in principle, to have equal entitlement to participate. The state-centred model instead rests on the administrative power that a political majority is able to mobilise to back-up its wills and interests. Moreover, legally enforceable regulations only need to publicly exhibit formal coherence with the rest of the existing legislation. They, in other words, can let the intentions and reasons of the legislator remain black-boxed and invisible to the public, with no formal detriment to their enforceability.

With the shared mode of regulation, instead, publicity can serve the ends of making policy choices more acceptable, and to stimulate multiple stakeholder to participate and contribute to the construction of the regulatory order. This is not a guarantee, however, that a genuine attitude towards publicity will actually inform the activity of scientific regulatory bodies and scientific societies. As a matter of fact, when scientists and other specialists gather at bureaucratic locations, they certainly run the risk

of behaving like an elite that does not have direct duties of accountability to very much wider publics. It has to be said, nonetheless, that many guidelines and regulations of acceptable stem cell clinical translation stress the importance of open public engagement, and sometimes take measures to organize that. In this sense, they go in the right direction but we have to wait and see to which degree these intentions will effectively be enacted.

As to the possibility to revise the normative arrangement that regulate science, the state-centred model, again, fares a bit worse than a self-regulatory one. In the case of embryonic research regulations, only changes in political conditions seemed to provide space for policy revision. Within the current regulatory framework of stem cell medicine instead, it seems that the normative arrangements remain fluid (Jasanoff 2011) so as to accommodate new technical acquisitions and new kinds of clinical trial applications, as well as the ethical implications that those novelties imply.

Finally, the language of policy-supporting arguments may in both cases be not functional to a deliberatively accountable discourse. Scientists might use their authority to appropriate the right to decide on scientific matters, thus excluding *a priori* all the non-expert as unfit to participate to the debate. This can be attained by, for instance, framing the stakes of stem cell clinical translation in exclusively technical terms, hiding the normative values that are touched by this thread of innovation underneath their specialised jargon. On the other hand, however, the state-centred approach to embryo-related research has been the stage of sustained efforts at undermining the moral and political legitimacy of opposing parties and at wisely using bits and pieces of scientific information to gain public support to one side or the other.

Now, the governance regime that is emerging around early efforts of stem cell clinical translation does not seem perfectly fit from a deliberative democracy standpoint.

If scientists play a prominent role in shaping the ethical and technical infrastructure of the incipient stem cell medicine, they are obviously doing it to the advantage of their own understanding of the problems that arise in the field. Inclusiveness and participation of wider publics might thus be overlooked, if this model heavily relies on expert advice.

It has to be noticed however, that lack of openness and accountability, beyond creating the conditions for possible violations of decent ethical standards, is not even in the interest of scientist-regulators themselves. As testified by the insistence of many guidance documents, publicity, inclusion and openness to revisions and improvements figure among cherished characteristics of this regulatory model. At any rate, in the future of clinical stem cell research failures and casualties are, at the very least, as likely to happen as in other fields of drug and therapy development. Being able to absorb such adverse events is thus perceived as a necessity by the entire field of stem cell research. If those failures have to occur, and they will – it is reasonable to expect – they must occur in the context of a fairly stabilized governance regime. My opinion is that introducing deliberatively accountable features into the governance model of stem cell translational research will be conducive to a less contentious and more legitimate climate for the advancement of stem cell medicine.

It is thus of crucial importance for the entire field, and for the promises it holds, that the deliberative intentions of the shared model be fulfilled to the greatest extent.

Stakeholders have to be engaged in the ongoing process of construction of the regulatory conditions of stem cell translational research. This can obviously be attained in

a variety of ways, but it is of the upmost importance that no epistemic dominance is exercised with the aim of excluding dissenting voices or to force the direction of governance towards the interests of powerful actors.

In this last respect, it has to be reminded that stem cell clinical research is not only a scientifically exciting field of innovation, but also a potentially profitable enterprise for commercially oriented stakeholders.

Intermezzo: Stepwise and frontier medical research

I said in the last sections of the previous chapter that state-driven initiatives are sharing the burden of control on stem cell innovation with scientific self-regulation. In this *Intermezzo* I want to introduce the reader to the material of the next chapter by showing that specific uncertainties afflict the shared-model of governance, as to the framing of stem cell innovation. The next chapter will show how commercial interests and epistemic commitments are pushing the governance model that I described and analysed thus far in contrasting directions. I will thus track the emergence of competing translational models for stem cell innovation and account for their respective political characteristics.

A defining feature of the shared model is its reliance on cherished epistemic virtues, scientific expertise, peer-review and evidence-based methods of acquiring medical knowledge. For reasons of prudence, as much as for reasons of scientific soundness, the development of new stem cell therapies is therefore provided within the framework of the same stepwise process that characterized the delivery of new drugs from the bench-side to the market in the last three decades. The globally adopted paradigm of drug development comprises a staged procedure that goes from systematic preclinical studies on animal models, to controlled toxicological analysis on limited numbers of patients or healthy volunteers (Phase I), to then progress to test efficacy in much larger cohorts in comparison with the existing standard of care or a placebo (Phase II and III). Regulatory agencies oversee the entire process, up to final marketing approval and post-authorization monitoring. Stem cell treatment would fall into this regulatory

pipeline notwithstanding the fact that, strictly speaking, stem cells are not drugs. However, it is indeed possible to consider stem cells as biologicals, therefore assimilating the regulatory route of their development to that of the latter.

In a recent thought provoking paper, David Magnus highlighted that, albeit such model is globally acclaimed to yield the most reliable scientific information on safety and efficacy of new treatments, it is not the only accepted methodology to advance medicine: "surgical innovation (in contrast to drug development) has tended to proceed by far less formal protocols and often outside the scope of regulation" (Magnus 2010, 267). Magnus interestingly classifies clinical trials according to the type of intervention that they imply and especially the amount and the kind of knowledge that researchers possess at the moment of recruiting research subjects. He thus recognizes three types of clinical trials: first in human (when an intervention under investigation is performed in humans for the first time), first in class (when the trial is not only first in human, but also "the first intervention using the particular type of mechanism", e.g. a new class of drugs), first in kind (when the trial is not only first in class, but also involves a new kind of intervention) (Magnus 2010, 268). In first in human and first in class clinical trials, "there is significant basis for believing that there is a certain probability of success in going from Phase I to Phase III" (*ibidem*). The author also calls first in kind clinical trials "frontier research", thus intending that those trials "are sufficiently different from other kinds of approved interventions in clinical use, meaning that there exists insufficient evidence for any kind of claims about the probability (or even the possibility) of going from Phase I to Phase III" (*ibidem*). Examples of frontier research include early attempts at organ transplantation or gene therapy research. It is moreover evident that early attempts at transplanting stem research at the clinical level also may be labelled as frontier research. With stem cell clinical trials, for the first time, cells with some degree of differentiative potential, or their

terminally differentiated progeny, grown from embryonic or otherwise obtained pluripotent progenitors, and possibly harbouring genetic modifications, may be administered to target human pathologies that were never treated in this way before. The doctors and scientists involved in these developments thus rightfully envisage a remarkable degree of novelty in this respect. Magnus however, argues that being frontier research, stem cell clinical translation might avail itself of additional ethical provisions that, albeit, in his opinion, not required by the normative arrangements governing drug development, may smooth the pathway to stem cell therapy from a moral standpoint. He thus recalls four ethical norms that were initially proposed as adequate safeguards for innovative surgery – possibly a paradigm case of frontier research. Drawing on earlier work by Francis Moore, Magnus establishes the following additional moral indications for stem cell frontier research:

1. Preclinical data must show that evidence is sufficient to grant switching to clinical research as reasonable;

2. The involved institutions must show adequate institutional field strength, i.e. they must have resources and personnel necessary to minimize risks to research participants:

3. For the trial to take place, adequate ethical oversight and consultative capacity must be assured (allegedly by the presence of dedicated personnel in IRBs);

4. Both the professional community and the public have to be openly informed before innovation can take place.

Now, to the merit of this proposal, I think a couple of objections could be moved. First, there is already reference to all the above listed points in nearly all regulatory documents on the development of non-frontier research. Secondly, surgical "frontier" innovation is indeed a valuable source of medical improvement, but it requires additional moral provisions exactly because it does not take place within the formal framework of the stepwise process of EBM. This is not to say that regular clinical trials are free of any further moral complication. Stem cell clinical research, for instance, regardless the adopted translational model (be it formal or frontier clinical innovation), presents a number of additional ethical problems that are not directly covered by the existing moral framework for the protection of human research subjects. To list but the most striking, alongside with the already mentioned technical limitations in assuring cell purity, stem cell research presents some special problems with respect to informed consent and therapeutic misconception. In particular, the risk of therapeutic misconception (Appelbaum, Roth, and Lidz 1982) is remarkably more acute in a field that, like stem cell research, appears to harbour much hyped expectations on the part of potential patients and the general public as well.

Hence, in my view, Magnus' suggestion to apply additional provisions to stem cell clinical development, is not in itself worthless. However, I do not think that the specific concerns of stem cell translation map entirely onto the distinction between conventional and frontier clinical research, as Magnus seems to argue. On the contrary, although I agree that stem cell clinical research qualifies as frontier research, I see its specific ethical problems arising from the nature of current technical limitations and not from simply sharing features of novelty with surgical innovation. In particular, as it will emerge in the next chapter, a limiting factor to go ahead with stem cell clinical research in ethically safe ways is the still limited amount of scientific information about the biological properties of

stem cells once re-injected *in vivo*. Notwithstanding the remarkable efforts of research groups around the world, we still have to learn a lot about stem cell biology to fully exploit their potential from the therapeutic point of view. It is therefore only scientific knowledge that, in theory, can be conducive to ethically less risky uses of stem cells in humans. It is obvious however, that such knowledge can only be obtained by coupling rigorous *in vitro* research with experimentally controlled pilot studies in animal models and, most importantly, in human subjects. Now, the additional criteria proposed by Magnus allude to principles of reasonable conduct with respect to the availability or lack of sufficient scientific information about safety and efficacy. His reasoning, however, is affected by some evident circularity: if the problem with frontier research is lack of systematic scientific information about safety and efficacy in humans, requiring this information as the basis of the special moral provisions of frontier research is incoherent.

Biomedical innovation thus faces a dilemma: on the one hand, present scientific uncertainties generate the need for special moral oversight; on the other, the implementation of those special principles requires exactly the kind of knowledge that currently lacks and makes them necessary. Magnus' paper, therefore, provides an unsatisfactory answer, or more precisely, an unsatisfactory approach to the translational dilemma of biomedical innovation. However, it touches on a very interesting dichotomy between the stepwise and the frontier model – one that is playing an increasingly prominent role in the current debate on stem cell translation.

As a matter of fact, as we will see in the next chapter, the choice between different translational models (i.e. stepwise clinical trials and surgical innovation), and thus between different framings of stem cell therapy development (as new biological drugs or as tissues to be used in a surgical context) is turning into a harsh debate about different understandings of the notions of risk, safety, scientific authority and knowledge

certification. In the course of the next chapter I will therefore illustrate how the governance of stem cell medicine is coping with an ascending disagreement over the possibility to adopt one translational model or the other.

Chapter 4: Contesting the governance of stem cell innovation

Notwithstanding efforts at designing a specific form of governance for stem cell innovation, harsh controversies characterised recent developments in the use of stem cells for clinical purposes. In this chapter I will account for those episodes of stem cell innovation that are challenging the shared-model of governance described in the previous chapter. I will show how national borders are being exploited to both exert order on stem cell innovation and to transgress existing regulations (4.1). In 4.2, I will describe the construction and deconstruction of scientific credibility by actors engaged in the development of alternative framings of stem cell therapy. In 4.3, I will explain how controlled clinical trials are being framed to bring these divisions under control, and I will analyse their import on the credibility cycle of the shared-model of governance.

A recent case will introduce an instance of the divisions that are emerging in the field of stem cell clinical application. Texas Republican Governor Rick Perry is not a new name in the debate on biomedicine. Three times Governor Perry hit the headlines in 2007, when he issued an executive order to make Human Papilloma Virus (HPV) vaccination mandatory to 11-12 year-old girls in the State. Revelations of vaccine

producing companies financially backing Perry's gubernatorial campaigns later resulted in a political scandal.[9]. Recently, he took the stage of a biomedical controversy once again, sending a letter to the Texas Medical Board (TMB) on July the 25th 2011. In this letter, the Governor pleaded for TMB to take initiative in order to make Texas "the world's leader in the research and use of adult stem cells" (Office of the Governor, 2011).

A consumer of expensive autologous stem cell injections himself, Perry called for the pursuit of autologous adult stem cell procedures as a promising way to treat "arthritis, orthopedic conditions, cardiovascular disease, […] diabetes, […] autoimmune diseases, leukemia, and other types of cancer" (Office of the Governor, 2011). He thus invited TMB to consider the alleged therapeutic virtues of autologous adult stem cell therapy while drafting regulations on these matters.

The latter sparked quite a number of reactions within the scientific community, mostly expressing concerns for the Governor's invitation reflecting a simple-minded attitude towards the meaning and the epistemic rules of medical innovation. Rushing stem cells to the bed-side, many scientists argued, is unlikely to do any good to the advancement of the field (Cyranoski 2011). Indeed, it may well undermine the chances to turn stem cell knowledge into stem cell treatments for two interconnected reasons. First, autologous treatments for an array of unrelated conditions, other then being generally questionable from a medical point of view, aim at producing curative effects on individual patients, and not at gaining generalizable knowledge on the applicability of a given procedure to a large group of patients – that is to say, the actual pay-off that medical scientists expect from EBM controlled clinical trials (CCTs). Stem cell scientists are therefore worried that unscrupulous practitioners might, on the one hand, fool patients

[9] I acknowledge my colleague Paolo Maugeri for information and insightful discussions on the HPV controversy that, unfortunately, I cannot discuss much further in this dissertation.

with unproven therapeutic promises or, on the other hand, exploit patients as research subjects to short-cut the time consuming and costly procedures that CCTs demand.

A second matter of concern for scientists commenting on autologous adult stem cell injections is that, were those treatments to result in severe adverse events, the whole field of stem cell clinical research risks to be seriously undermined in terms of credibility.

Notwithstanding these reserves, we will probably see the state of Texas adopting liberal provisions with respect to adult stem cell direct application to the clinical context in the imminent future.

The episode recalled here is but a latest occasion of tension between the certified stem cell community and practitioners who either already sell alleged stem cell treatments to consumers worldwide, or try to bypass the regulatory bottlenecks of canonical CCTs therefore exposing research subjects to risks that are generally considered unethical. Let us then try get to know a bit more about such phenomenon, and learn how the demarcation of genuine scientific research from unproven stem cell treatments leads to the construction of certified stem cell knowledge and to the emergence of competing translational models. We will see that a 'regulatory order' (Kent *et al.* 2006) is being crafted around these separations, but also that, to a remarkable extent, the latter are indeed a result of the existing regulatory order or, better said, of the blank spaces that it leaves available. Again, in the case of stem cell translation, efforts at institutional stabilisation and diverse epistemic commitments conjure to give rise to a 'regulatory order' that remains in tension between competing interests and different modes of agency.

4.1 The borders of validity

The landscape of stem cell clinics offering professed treatments with cellular products is wide and uncharted. It is estimated that at least 200 clinics exist in the world that offer stem cell treatments and/or slots in stem cell clinical trials (Anon. 2010). Attempting to compile a comprehensive catalogue thereof would thus be hopeless. In this section I will therefore report on selected episodes of stem cell clinical transplantation that gained public attention due to controversial outcomes and/or institutional conflicts. I will include clinics offering stem cell therapies in China (4.1.1), as well as in the US (4.1.2). Furthermore I will illustrate under which conditions analogous procedures could be possible in Europe (4.1.3) and how existing differences between different national regulations are being commercially exploited in what has been called stem cell tourism (4.1.4).

The cases that I will describe will serve as a compass to later orient analysis into the territory of marketed stem cell treatments. I will therefore use the word 'treatment' to indicate any attempt at injecting cellular concoctions into human patients, irrespective of the actual medical efficacy that can be attributed to those practices. When I will speak of 'adult stem cell transplantations', moreover, I will not mean that to include bone marrow (BM) grafts for blood-related conditions that already enjoy widespread acceptance within both the medical community and the regulatory system.

4.1.1 Exotic stem cell treatments

In the last decade, thousands of people received stem cell injections in dedicated private clinics at their own expenses. Stem cell centres are active in the US and also in

Europe, but most of these clinics are reported to be in China or in other remote locations in Asia, Central America and Eastern Europe. The typology of those cellular products ranges from foetal parts to human embryonic cells, to autologous adult stem cells of various origin. The research community has been rather consistent in considering those treatments as scientifically unproven, medically unjustified, and ethically unwarranted. An international market of adult stem cell therapies nevertheless arose. Stem cell clinics generally offer their services over the Internet, through web sites that explain the presumed advantages of the offered interventions over more canonical alternatives, and providing the means for a first contact between the clinic and the patient.

A major reason of consideration for patients who resort to stem cell clinics has always been the absence of satisfying cures for their medical conditions. It is therefore almost natural that patients with tragically impairing or life-threatening diseases figure among the most typical consumers of stem cell treatments. The business of stem cell treatments thus proved particularly prolific with neurodegenerative disorders (such as ASL), spinal cord injury, and certain kinds of cancer. Patients affected by such debilitating diseases and their families are often desperate enough to start looking for therapeutic alternatives and for free slots in experimental clinical trials, even if these meant travelling to distant locations and paying high fares to receive the hoped for procedure.

Let us take spinal cord injury as our entry point into the world of stem cell clinics.

Following trauma, such as ones occurring in car accidents, a person's spine may be injured so as to provoke paraplegia or even tetraplegia, depending on the site of the injury. There is currently no recovery from these conditions and, often, affected people need life-sustaining machines, like ventilators, and dedicated personal assistance to just keep on living. Animal model studies have been published showing preliminary results

with cellular therapy for spinal cord injury (Li, Field, and Raisman 1997; Ramon-Cueto *et al.* 2000; Li, Decherchi, and Raisman 2003). These studies used olfactory ensheathing cells (OECs) to promote some functional recovery in rat models of spinal cord injury. Based on these results, Dr. Hongyun Huang, a neurologist at the Chaoyang hospital of Beijing, started to use OECs from aborted human foetuses in spinal cord injured and ASL patients. It is estimated that he treated some 600 people in five years between 2001 and 2006 (Huang *et al.* 2009). Many of those patients, pushed by their desperate conditions, travelled to Beijing from all over the world, spending some 20.000 $ each to receive the treatment (Cyranoski 2005). This phenomenon whereby people travel to distant clinics at their own expenses to obtain unconventional treatments is generally referred to as 'stem cell tourism'. Huang repeatedly reported many of his patients enjoyed improvements after the surgery, but external observers and peer-reviewers who refused to publish his results on mainstream medical journals, maintain that no measurable data support Huang's claims other than anecdotal testimony from some patients themselves. Most commentators thus discarded Hung's procedure as lacking efficacy, and being too risky and too unjustifiably expensive for patients. As a matter of fact, Huang's incapacity to meet the technical, not to speak of the ethical, standards of the international medical community, was used as a criterion for carving a demarcation between legitimate and illegitimate clinical procedures, thus serving the construction of a unifying identity for the emerging stem cell community. Surely, this image had geographical connotations that mapped onto the regulatory differences that permit in China what is strictly prohibited in many Western countries. The geographical divide between Chinese and the Western-based journals that refused to certify Huang's interventions as scientifically sound and therapeutically valid was also a direct matter of polemic exchanges. In an interview to Nature, Huang accused the *British Medical Journal*, *Nature Medicine*, the *New England*

Journal of Medicine, *Science* and *The Lancet*, of rejecting his papers on the basis of a prejudice against watershed medical innovation coming from Chinese researchers (Cyranoski 2005). In 2006, a panel of specialists conducted an independent inquiry on seven of Huang's patients (Dobkin, Curt, and Guest 2006) reporting "perioperative morbidity and lack of functional benefits" (*ivi*, 5), thus concluding that "[u]ntil international standards for scientific trial methodologies have been incorporated, clinicians are obligated to advise their patients to forgo Dr Huang's procedure" (*ivi*, 13).

The Huang controversy illustrates the use of peer-review standards of knowledge certification as a tool to demarcate epistemic and normative standards at the same time. The dispute took the form of a contention about the reliability of the peer-reviewing system.

In particular, during international conferences, Huang used videotaped patient's own reporting on alleged benefits due to the procedure (Cyranoski 2005), but this is generally deemed an unreliable sources for probing clinical validity. Moreover, in the paper he published to make the case for the utility of his procedures, Huang and his team fall short of abiding by the canonical phasing of controlled clinical trials [10]. Thus, irreconcilable views on what counts as sound clinical research put discussants at the opposing poles of the dispute. Critics instead, saw insurmountable flaws in Huang's unorthodox way of gathering evidence in favour of its procedure.

But at stake here was not only the medical validity of Huang's procedure. In a clear display of a co-productive dynamic, the protagonists of this quarrel were espousing contrasted normative commitments about the ethical liability of the procedure as well.

[10] It has also to be recalled that Huang's publications are mainly in Chinese, and that only a English-written abstract is available over the Internet presenting the results from his OEC procedures. See Huang *et al.* 2009, available here.

Differing considerations about the ethical treatment of research subjects and patients were indeed crucial. Dr. Huang defended his procedure as being approved by the Beijing hospital ethical review board, and insisted on the urgent necessity to give hopeless patients a chance with an innovative treatment. On the other hand, critics insisted that the treatments were not peer-reviewed as to neither safety nor efficacy. In the absence of expert oversight, patients were thus exposed to unjustified risks and superfluous costs. Inability to meet safety and efficacy standards was an ethically grave allegation, but Dr. Huang thought his patients had a right to receive an innovative treatment that Western medicine wanted to deny. The medical community, instead, stressed the right to protection from unnecessary risks that clinical subject and patients are entitled to, and that only abidance by international standards and peer-review methods are able to guarantee. Outside the stepwise procedures of CCTs, critics argued, patient's hopes are irresponsibly exploited to the financial advantage of the clinic.

The quarrel thus revolved around both ethical and clinical validity, and relied on diverging notions of patient's rights and expectations in the clinical context. Such dispute reinforced the severing of mainstream science from uncertified clinical approaches, and exhibited science's capacity to watchdog its borders. The categories of 'unproven treatments' and 'stem cell tourism' were being forged to construct firmer boundaries around official peer-reviewed stem cell research. Disputes over the legitimacy of unproven treatments thus saw part of the global stem cell community engaged in sturdy exercises of boundary-work. The necessity to build up a credible image of responsible stem cell research was at the origin of the creation of the ISSCR, and drove the drafting of the Guidelines that I mentioned in the previous chapter. Such proactive engagement of the scientific community into the medical and ethical dimension of unproven clinical

practices, also ultimately reflects the 'regulatory vacuum' (Faulkner *et al.* 2003; Faulkner 2009) that characterises stem cell-related products and practices.

In this empty space, however, normative ideas are articulated and intertwined with epistemic and procedural commitments. The methodologies of biomedical research and practice thus have the function to create, at the same junction, scientific and regulatory order around the circulation of stem cell entities in the clinical setting. These dynamics serve the creation and reinforcement of scientific membership and are used to back power claims on the steering of the entire field. Accreditation and exclusion criteria, notions of risk and safety standards shape the formation of a transnational epistemic community and bring order into the unruled territory of stem cell clinical applications. As the Chinese story testifies, regulatory loopholes and national differences prevent order-making practices of scientific and ethical certification from fully stabilising a definite regulatory regime around stem cells. For this reason, some scholars have found it more appropriate, in the case of unstable innovative biomedical technologies, to speak of 'regulatory order', rather than 'regulatory regime', to stress the scarcely formalised "web of interlinked laws, regulations, guidance, surveillance and other behaviours which might 'govern' particular technologies" (Faulkner *et al.* 2005).

4.1.2 How manipulation matters

The rise of stem cell clinics is a phenomenon that is caused by the technical progress of the life sciences. Furthermore the phenomenon is reinforced by the hype that surrounds the promise of stem cell science and that, to a great extent, the research community can no longer control. There is no doubt, however, that the proliferation of stem cells being offered on the clinical market, and the controversies that it elicits within

the scientific community are also the result of the regulatory vacuum that I mentioned above. Commentators have stressed that a hybrid character is typical of novel biotechnological procedures like tissue engineering, gene therapy and stem cells, as these novelties hardly qualify as medicines or devices in a strict sense. This deprives regulatory authorities of the possibility to properly exert control on the development of clinical procedures relative to the advanced medical approaches. We saw in the previous chapter that such uncertainty led regulators to take measures and adopt arrangements to normalise the governance of advanced therapies. With respect to stem cells, one standard regulatory strategy is to classify them as biologics, so as to extend on them the regulatory powers that governing bodies already have on this class of products. It has nevertheless to be stressed that the regulatory order that is being developed around stem cells still falls short of leaving no gaps to be filled. As a consequence, conflicts still arise and are likely to arise in the future. In this respect, it is important to stress that the institutional identity of regulatory agencies, and the scientific credibility of stem cell scientists, rather than being pre-given variables of those conflicts, are in the midst of being crafted throughout these litigations.

A recent example illustrates this dynamics in a fairly clear manner. Regenerative Sciences, is a stem cell clinic based in Broomfield, Colorado. In early August 2008, its medical director Dr. Christopher Centeno found himself in the eye of a legal and scientific tornado. His clinics had been offering autologous adult stem cell injections to patients for some years, at a price of around $ 8.000 per shot.

In a same-day procedure Regenerative Sciences draws marrow and/or blood from patients and then re-injects those stem cell-containing aspirates at different bodily sites depending on the pathology they intend to cure. This thus qualifies as an autologous adult stem cell transplant. On their website they describe the procedure as a shot of

mesenchymal stem cells (i.e. progenitors of bone, cartilage and fat) and blood platelet lysate that allegedly should treat joint, bone, cartilage, ligament and tendon problems. In the absence of purification procedures, the aspirates are more than likely to contain much more than just mesenchymal stem cells. This impurity however, in the intentions of Dr. Centeno, works as the escape valve to avoid FDA claiming regulatory control of his stem cell therapies. According to the already mentioned Code of Federal Regulations (1271.10) clinical use of stem cells is not regulated by the FDA if cell-donor and cell-receiver coincide, and if the cells in question are only minimally manipulated.

It was thus exploiting this sort of gap in regulation that Regenerative Sciences could offer their treatments on the market.

FDA tried to object that stem cells used by Centeno and colleagues, belonging to the trademarked Regenexx product family[11], were to be treated as drugs (namely biological products) under the Public Health Service Act. Centeno, on his part, instead insisted that his was a medical procedure for which FDA oversight did not apply.

However, when Regenerative Science started offering more than minimally manipulated cells, the Department of Justice, on behalf of FDA, filed an injunction in the US District Court for the District of Columbia to halt Centeno. According to the injunction, Regenerative Sciences was now growing, processing and mixing cells with drugs before putting them back into patients without FDA approval, thus acting against the law on current good manufacturing practices (cGMP). Centeno replied that, although he was not acting under FDA oversight, he was on safe grounds for he followed the guidelines of the

[11] The characterisation of Regenexx cells as a "product family" is taken from the original wording of the company itself. It has to be stressed, however, that this is simply a commercial label that refers to the allegedly unique procedures that Centeno's clinic employs to derive stem cells.

International Cellular Medicine Society (ICMS), that I mentioned already in the previous chapter and that I will analyse in depth shortly in the present one.

It is interesting to highlight here how existing regulatory bottlenecks, and fears of FDA interference, ended up building the very constitution and marketing strategy of the Regenexx product family. As it is clearly observable from the company's website, Regenexx is a trademarked name attached to a group of cellular products sold and administered by Regenerative Sciences. Images of people hiking muddy pathways or professional sport sequences scroll on the upper side of the webpage where Regenexx cellular products are presented. Along with them, testimonies report about the therapeutic virtues of the Regenexx family. The company is thus evidently focussing on bone and joint injury applications. The Regenexx product line includes: Regenexx SD (same day), bone marrow cells extracted and implanted on a same-day procedure; Regenexx AD (adipose derived), allegedly fixes meniscus injury via a structural fat graft; and Regenexx C (cultured). The latter are cultured stem cells, about which the website does not provide further information, apart form saying that they are available at the company's non-US site in the Cayman Island. As I said above, the Regenexx product family thus incorporate the regulatory restrictions on cellular therapies within its very articulation. In a quite literal sense, Regenexx represents the material embodiment of existing regulatory loopholes and alternative framings of the epistemic and, as I will show in the coming section, normative stakes of cellular therapy.

Regulatory paternalism

When *Nature* reported the news of the FDA injunction against Centeno, some patients started to post comments on the journal's website that deserve a closer look.

A terminally ill patient, for instance, claimed that “the practice of medicine really needs to be between a doctor and his patient” and that “to not allow autologous stem cell treatments for the terminally ill in [US] is a travesty”. As to FDA’s injunction the same patient commented: “[p]atients are left wondering why the scientific community fails to ever consider what we want”. Along the same lines, another comment “applaud[ed] Regenerative Sciences for standing up to the FDA […] it is about time someone did”; and added “[w]e must stand up for our rights as patients and if our very own cells are not ours I don’t know what is”; thus concluding “[i]t should be up to me and my doctor to decide what is the best treatment for me not a government agency”.

Those persons are clearly stating an individual right to be treated according to their perceived medical needs and therapeutic preferences. Notably, such right is being articulated in an adversarial fashion towards centralised regulation, governmental interference, and medical paternalism. FDA activity is perceived as bearing diverging ends with respect to the therapeutic rights of patients. It is indeed interesting to notice a shift in the articulation of medical paternalism in those comments. Typically, medical paternalism refers to the overwhelming authority of physicians who tend to disregard patients’ autonomy and their willingness to participate proactively to the therapeutic decisions, allegedly, in the interest of the patient herself. In this instance however, paternalist allegations are not directed to the practising doctor, but to biomedical researchers and their associated governmental agencies who impose their views on how innovative practices should proceed onto the legitimate wills of patients. This new framing of medical paternalism, I propose, should be called ‘regulatory paternalism’, and represents a still uncharted territory for bioethicists to explore. Regulatory paternalism can thus be identified as the practice of setting up regulatory standards that incorporate specific ideas on how the medical research community and regulatory bodies should

protect the interests of research subjects and advanced therapy in the development of new therapeutic approaches. Discourses of protection thus intercept the procedural commitments of biomedical innovation engaging both the normative and the epistemic in the creation of social order around emerging biomedical technologies. According to regulatory paternalism, patients and research subjects are deemed incapable of autonomously assessing the risks associated with frontier research (Magnus 2010) and experimental treatments because their judgement is overshadowed by three limiting factors: 1) the lack of sufficient technical expertise on the methods of clinical research and medical progress, 2) the lack of sufficient technical expertise about the very procedures that they are offered, and 3) the trumping desire to do something about their medical conditions that often, although not always, are characterised by extreme severity and very poor prognoses. In other words, patients and research subjects are deemed to be in conditions that are sub-optimal in terms of decision-making rationality, a condition that only strict ethical and regulatory oversight can attempt to remedy. On the other hand, the research community and the regulatory bodies see it as one of their fundamental missions to adhere to existing standards of patient/research subject protection and to do all they can to steer biomedical innovation under the aegis of comparably stringent standards.

Regulatory paternalism is contrasted with a rather cluttered set of affirmations about individual autonomy and liberal rights of freedom from governmental intrusion in private matters. These claims thus depend on imagining the fight against one's illness as a sort of citizen-consumer choice of therapeutic options available on the market. Restoring health thus becomes a commercial transaction between the patients and the providers of medical services – one that regulatory oversight can only impede or slow down, and that the research community unjustifiably contrasts. Those who frame their claims in

opposition to regulatory paternalism, see their freedom curtailed by regulation, oversight and, especially, by scientists' abidance by the stepwise model of medical innovation implicit in the CCTs. Conceptualising the therapeutic relation as a private one to which the state has no stake in intervening, is in tune with narratives depicting regulatory agency as biased in their activity by connections with private interests. Frustrated by the gravity of their condition, patients can indeed be brought to interpret the slow pace of scientific research not only as a matter of clumsy regulatory activity, but also as a direct consequence of a mischievous triangulation between the pharmaceutical industry, scientists and the government. Compliance with standards of safety and efficacy assessment, thus comes to be deconstructed as a tool for exerting control, both political and commercial, on an emerging field of biomedical innovation.

By the same token, ICMS representatives, for instance, cleverly framed their position also as an attack to presumed links between FDA, ISSCR and the drug industry. In an open letter reported by *Nature*, ICMS accused the ISSCR of opposing stem cell treatments due to its ties with pharmaceutical firms. The rationale for such accusation is that ISSCR is partly funded by the industry[12] and autologous therapies of the kind performed by Regenerative Sciences do not promise much profit for drug firms. At this junction, the as yet uncertain material constitution of stem cell therapies intercepts the financial expectations of the private investors who put money in the field in exchange of expected revenues. The administration of autologous stem cell therapy however, only produces revenues for the clinics that perform it. The most profitable way for the industry to squeeze income out of stem cells, instead, is selling cell lines as IP-protected products, which is best served by heterologous treatments using patented stem cells. ICMS thus conjectured that the industry, backed-up by FDA watchdogs and speaking through ISSCR

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members, may act so as to prevent the field from taking the direction of homologous patient-to-patient cell treatments. Such allegations reinforced a narrative of denied rights, diffidence towards governmental agencies, and suspicion for certified science that feeds the recriminations of wannabe stem cell patients and clinicians[13].

The articulation of regulatory paternalism, and of its critique, can be viewed against the background of a more general transformation of the practice of health care provision into a commercially oriented activity. In a recent letter to the New England Journal of Medicine (NEJM), Hartzband and Groopman, highlighted the silent adoption of a commercial language in the medical community as a sign of this transformation (that they see as deleterious)[14]:

> «The relationship between doctors, nurses or any other medical profession and the patients they care for are now cast primarily in terms of a commercial transaction. The consumer or costumer is the buyer, and the provider is the vendor or seller» (Hartzband and Groopman 2011, 1372).

In this context, on the one hand, regulatory paternalism is but one instantiation of a wider phenomenon that sees medicine increasingly entangled to the very culture of commercial firms – as the perceived shift in language is suppose to reveal. On the other hand, however, the critics of regulatory paternalism wave an image of patients that

[13] Having read the content of Regenerative Science website, and of many other similar organizations, I myself formed the belief that, from a scientific point of view, what these clinics offer is unconvincing. The reserves of ISSCR scientists, instead, appear to me to be justified. Furthermore, I think that conceiving of therapies as totally embedded in an exclusive relationship between doctors and patients, reveals a fundamental misunderstanding of the inner workings and social function of modern medicine as a collective enterprise for the advancement of people's welfare. As an analyst, however, I am committed to look at how identities, power relations, and regulatory authority emerge across these oppositions. This implies that, in the main text, I espouse a certain neutrality towards the claims I descirbe, notwithstanding my parting for scrupolous ethical and clinical oversight on the inevitably slow development of stem cell medicine.

[14] I acknowledge Giuseppe Testa for pointing this letter at me.

coincide exactly with that of an isolated consumer of heath goods. Therefore, from both sides, this confrontation seems internal to an overarching transformation in the way medicine is conceived and offered to individuals. To be sure, such cultural transition is taking multiple routes (e.g. through personalised medicine, pharmacogenetics, pharmacogenomics, direct-to-consumer genetic tests, and self-testing devices), but stem cell medicine, as the events recalled here testify, is likely to represent a privileged locus of its articulation.

The dispute I described in section 4.1.2, was thus the site of a major exercise in boundary work, whereby scientific credentials are distilled and contested, and different moral commitments contrasted in order to construct a line of separation between the orthodox scientific community backed by governmental agencies on one side, and practising stem cell clinicians interpreting the will of patients on the other.

This story, like the previous one, shows a dispute arising on the demarcation of science, regulatory authority, and patients' freedom. Terms like 'medical product', 'biologic', 'drug', 'manipulation', 'medical practice', 'GMP' were used by FDA to implement its authority, and by stem cell clinicians to legitimate their work and expertise. Individual patients, resonant with ICMS, framed their rights by projecting their frustration on government blocking research and on the allegedly inappropriate interests of scientific societies like ISSCR: the indubitable steering influence of science's industrial partners cast doubts on the credibility of the latter, thus creating an adversarial relationship between different actors and stakeholders.

Moreover, revealing industries' financial support to ISSCR, the quarrel shows that commercial actors are in the position to at least influence the form of stem cell medicine

based on the choice of the translational model that is more likely to produce profits, and that this possibility is exploited argumentatively to make the case against regulatory paternalism.

On this terrain, involved actors employed resources including interests, imaginaries, and moral outlooks that appear difficult to reconcile with one another. In particular, the contrasts here described typically take the form of quarrels on regulatory paternalism. The latter category thus emerged as a novel and important player for the articulation of contrastive innovation narratives and the construction of separate professional identities. We will see, later in this chapter (section 4.2.), how this notion played out in the disputes between ISSCR and ICMS on the certification of stem cell clinics.

4.1.3 European hospital exemptions: clinical validity across internal borders

Europe has similar but more articulated provisions than the States as to the possibility of injecting cellular products into human patients. I will show in the present section how the European Union uses its powers in regulating the internal circulation of medicinal products to enact a distinctive, albeit not fully specified, vision on the clinical validity of stem cell treatments.

The text of the 2007 regulation of the European Parliament and Council on Advanced Therapy Medicinal Products (ATMPs) amends previously existing provisions as to use of medicinal products in Europe.

The main effort of this regulatory tool is to construct cell therapy (and gene therapy and engineered tissues as well) as the provision of a medicinal product. As I already explained above, this strategy, whereby innovative medical possibilities are

defined, and thus regulated, as biological drugs, stands as a primary mode for exerting regulatory control over novel medical applications. The aim here is to normalise the presence of novelties by assimilating them to more familiar medical tools, thereby inscribing them, through classification, into an already existing normative order. Such strategy, however, rests on the difficult task of ordering novelty through a series of complex epistemic moves and un-obvious classificatory decisions.

In order to be taken as biological medicinal drugs, cellular products need to be framed out within a credible understanding of the activity of therapeutic agents in the human body. It is worth recalling here however, that epistemic resources of this kind cannot simply be retrieved from a body of shared medical notions. Rather, they have to be established *ad hoc* and, as a consequence, they remain open to possible contestations.

Thus, the classification of cellular products as biological medicinal drugs rests on the realisation that they are used "with a view to restoring, correcting or modifying physiological functions by exerting *principally* a pharmacological, immunological or metabolic action" (2) (emphasis added).

This vagueness as to the modes of action that define a biological medicinal product, thus leaves a door open for novel forms of biological activity that innovative therapies might exploit. In this way, the provision extends regulatory control to both present and future applications. Therefore, it is to accommodate to the uncertain character of novel therapies that the classification looks somewhat underdetermined. Hence again, in line with what I said in chapter 3, whereas the regulatory prerogatives of political actors in the governance of stem cell translation are challenged by the specific uncertainties and the intrinsic instability of these new medical products, European regulators left room for future applications to eventually fall within the scope of present

regulations. Framing cellular products as biological drugs, however, ultimately remains an open-ended process and, as I show below, requires further resources.

According to the 2007 amendments included in the EU Regulation on Advanced Therapy Medicinal Products, the dispensations of the 2001 Directive on Medicinal Products for Human Use do not cover gene therapy, cell therapy and engineered tissue, provided they are prepared

> "on a non-routine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive medical responsibility of a medical practitioner, in order to comply with an individual medical prescription, for a custom-made product for an individual patient" (2001/83 art 3 par 7 as amended by art 28 1397/2007).

This principle has come to be known as the 'hospital exemption' rule, thus stressing the idea that individual clinics can derogate from the European marketing authorisation procedures, provided certain technical conditions are met.

In a creative display of awareness about the co-productive nature of scientific policy, the hospital exemption rule exploits the very geographical peculiarity of the European Union to create and exert order in the field on innovative cellular therapies. As one can read from the quote above, it is intra-European borders that perform the new regulatory function here: the hospital exemption rule, albeit permitting a certain degree of therapeutic freedom, confines it to the individual state level. The borders that divide Member States are indeed being used as a tool to regulate, by actually limiting it, the circulation of unproven ATMPs within the Union. Unspoken considerations about clinical

validity thus intertwine with the statutory power of EU regulation to open up or close down the internal borders of the Union to the circulation of medicinal products.

Whereas in many previous examples it was national borders – porous to the circulation of both patients and cells – that allowed cellular products to be injected in human patients in different geographical locations, in the case of Europe borders play a strikingly opposite role. Here, borders are constructed as barriers to the possibility of practising stem cell therapy outside of regulated CCTs. The non-permeability of intra-European borders to unproven cell therapies forcefully contrasts with the overall intention of this piece of legislation – aimed at creating a common space for European scientists and patients alike to share knowledge, materials and, possibly, the benefits of pursuing biomedical innovation in a regulated manner. Whereas with respect to the latter European legislation plays a facilitating role, with respect to experimental treatments, it poses a territorial obstacle. In general, European regulations on medicinal products, including ATMPs, have the aim to harmonise and promote the free circulation of medicines within Europe, but, quite to the contrary, the hospital exemption rule constrains the presence of human cell for therapeutic use within the Member State where they were derived

The hospital exemption rule, however, does not explicitly endorse any clear-cut epistemic distinction between proven and unproven treatments. Nor does it set a standard for a minimal amount of pre-clinical and clinical evidence as to safety and efficacy. Nonetheless, it makes use of national borders as barriers – both epistemic and

normative – to limit the exercise of stem cell medicine outside accepted scientific methods of knowledge production and validation[15].

Thus also in Europe, like in the States, the amount of manipulation configures a technical boundary between acceptable and non-acceptable cellular treatment. At the same time, those criteria define the threshold of acceptable risk in the practice of stem cell medicine, by conceding that, minimally manipulated cells are unlikely to cause harm to patients. This last consideration, however, omits to take into due account the dependence of the safety profile of cell therapy upon cell type, immunological characteristic and site of injection.

At any rate, albeit ill-defined, criteria of non-routinized custom-made production seem apt to allow the exercise of acknowledged therapeutic practices, while at the same time limiting the scope of possible application of unproven cellular treatments. In this respect, however, the phenomenon of stem cell tourism, still appears to be possible within Europe, at least as far as hospital exemption concedes in terms of technical possibilities.

4.1.4 Border crossing for stem cells

I already mentioned the phenomenon of stem cell tourism in the previous sections. Travelling for cures, however, is not specific of stem cell medicine, nor it is of innovative therapies. As a matter of fact, patients travel, and have always travelled, for

[15] The reason why, at the national level, experimental treatments remain possible, is probably attributable to the fact that the 2007 legislation did not want to put extra burdens on standard-of-care human tissue-based interventions – like blood transfusions, BM and organ transplantations and IVF treatments – by introducing unsuited special provisions that would hinder their practice.

By so doing, however, the legislator left loopholes open in the regulatory framework that remind those already discussed in the previous section speaking of the US, and that, in theory, could still make certain kinds of stem cell treatments with minimally manipulated infusions possible at the national level.

undertaking advanced surgical interventions, for joining clinical trials in the hope of gaining some benefits, for performing IVF or, more simply, for obtaining the same medical treatment at a discounted rate. The latter phenomenon has grown especially in the proximity of national borders, such as that between the US and Mexico, where travelling is logistically less demanding for uninsured US citizens, as well as more rewarding financially for providers.

As to stem cell medicine, cross-border medical tourism took advantage of the differences in national regulation to offer off-shore stem cell treatments to patient-customers coming from more stringently regulated countries. I will now provide a few examples of stem cell clinics that operate across national borders to avoid unfavourable regulations.

One such case is that of the *Stem Cell Treatment Institute*. They provide autologous bone marrow transplant using tissue taken from hip bone, but also heterologous ("younger", as they say) cells from cord blood, placenta and adipose tissue. Those cellular products are supposed to "treat cancer, spinal cord, autoimmune diseases, Alzheimer's, cerebral palsy, diabetes, stroke, muscular dystrophy, heart failure". Their web site also claims the cells to be enhanced/activated by chemical "transfer factors". The cells used in these procedures are extracted in San Diego, CA, but they are then injected in a cognate clinic just off the border in Mexico.

Korean *RNL Bio* went a step further in internationalising its activities. They extract bone marrow and bank cells in the US and in Germany; they ship them to Korea for isolation and expansion; and finally they send their patients in China, Japan, Mexico and Germany for infusion. The company claims its treatments are indicated for 'de-aging', rheumatic conditions, atopy and stroke.

Bio-cellular Research Organization Inc. is based in the US, but it has offices and manufacturing facilities in Slovakia, Malaysia, Taiwan, India and Switzerland. They offer stem cells extracted from foetal and new-born rabbits and, interestingly, they ship them worldwide. According to their website, they recommend their cells for treating "diabetes and its complications, hormone deficiencies, early menopause, male and female infertility, spinal cord injury, Parkinson's disease, etc." (ref).

Progencell is instead based in Mexico, but advertises its treatments in English on its website and clearly addresses American costumers who can easily travel to Mexico.

The Institute of Cell Therapy has its headquarters in Kiev, Ukraine, but also opened offices in London and in the US. They offer autologous bone marrow transplants, as well as heterologous placental stem cells for "stroke, consequences of craniocerebral traumas, disseminated sclerosis, pancreatic diabetes, joints diseases, cardio-vascular diseases, hepatitis, liver cirrhosis, rehabilitation after chemotherapy and others" (http://www.stemcellclinic.com/en.html).

Global Laboratories LLC's founder and owner Fredda Branyon recently found herself in the eye of judicial case for selling cells over US State borders. According to the FDA's Office of Criminal Investigations (OCI) and the FBI's San Antonio Field Office, between February 2009 and April 2010, the Arizona based corporation sold vials containing stem cells to an individual in Brownsville, Texas, who later administered the cells to patients suffering autoimmune diseases. The total revenue from the traffic was $ 300.000, according to the investigators. August the 18th 2011, Braynon was charged and convicted for this by the Southern District of Texas. Branyon admitted of the allegations and currently awaits judgement on November 18th 2011. It is interesting to highlight FDA-FBI's framing of the case. The accusation states that *Global Laboratories LLC* trafficked

unapproved new drugs. It thus used a classificatory strategy to frame stem cells as a drug, instead of conceiving them as tissue. This is part and parcel with FDA's attitude in other cases described in this chapter. In the Brayon case, FDA again can avails itself of the Code of Federal Regulations (1271.10) to claim regulatory control over cell therapies. According to the law, heterologous stem cell treatments fall within FDA jurisdiction, thus the agency rightly convicted Global Laboratories' founder. What is worth stressing here, is that FDA took the occasion of the present case to restate its general attitude towards cellular therapies being offered to patients outside its legitimate control. In a press release, FDA-OCI's Special Agent in Charge Patrick J. Holland declared: "This criminal information demonstrates the commitment of the Food and Drug Administration to protect the American public from harms inherent in being exposed to unapproved new drugs. The FDA will continue to aggressively pursue perpetrators of such acts and ensure that they are punished to the full extent of law" (fda website). In this statement, Holland frames the role of FDA in terms of public protection, and constructs the image of the agency as the unique possible provider of such function. Furthermore, probably reminiscent of the Regenexx controversy, Holland delivered a muscular proof of FDA willingness to watch out for infringements of existing regulations. This boundary work exercise is finalised to deter profit-oriented clinics to play around with existing regulation, but also to diffuse the idea of the legitimate regulatory function of the agency within this field of biomedicine.

4.2 Designs on therapy

After having reported on controversies arising with early efforts at using stem cells in medical practice and clinical research, it is now time to see how these disputes configure the existence of radically different epistemic and normative commitments

towards the translation of stem cells from the bench to the bedside. This section will thus track the emergence of two contrasting attitudes with respect to stem cell translation. To do so, I will first reconstruct ISSCR efforts at contrasting the activity of stem cell clinics of the kind described above (4.2.1). Subsequently, I will show how narratives of patients' rights against regulatory paternalism found explicit articulation in the guidelines on clinical translation issued by the ICMS (4.2.2). I will then take the case of the UK Stem Cell Bank as a further instance of shared regulatory control over stem cell circulation, thus showing, once again, the plasticity of this governance model and its permeability to alternative framings of stem cell innovation (4.2.3). Finally, in section 4.3, I will speak to the role of controlled clinical trials in the management of clinical risk.

4.2.1 Patrolling clinical freedom

In this sub-section I will account for the kind of boundary work activity the ISSCR enacted to contrast clinical practice with unproven stem cell treatments, and for the contrasts that emerged around it.

Preliminarily, It is important to notice that the dispute here was made possible by the drift in the regulatory model that I described in the previous chapter. The scientific community took the lead in establishing criteria for responsible clinical conduct in the form of voluntary guidelines. But scientists, as it will also emerge in the next section, also gained prominence within regulatory bodies in the face of substantial legislative uncertainty over the governance of stem cell translation.

The case I will illustrate in the present section, speaks of the presence of two contrasting interpretations about how stem cell should be translated to the clinic. One side lines up the supporters of marketable clinical procedures mainly, but not uniquely, with autologous stem cells. On the other, critics of the safety and efficacy standards

adopted by stem cell clinics of this sort, praise for slow-paced and watchful translation through carefully designed, peer-reviewed CCTs.

In December 2008, together with the already mentioned Guidelines, ISSCR had already made a *Patient Handbook on Stem Cell Therapy* available on the Internet. This document, other then popularising a few basic notions on the biology of stem cells and their possible medical promise, warned patients of stem cell treatments if the providers failed to show: 1) peer-reviewed replicable preclinical studies, 2) the existence of an Institutional Review Board (IRB) or Ethics Review Board (ERB), 3) the approval of a regional or national regulatory agency. In addition, the handbook alerted patients to be particularly wary of stem cell treatment providers when patient testimony is the only base for efficacy and safety claims, the same cells are used to treat a multiplicity of conditions, clear documentation is missing as to the source of the cell or nature of the treatment, and risks are said to be absent.

In June 2010, ISSCR launched an initiative called “Submit a Clinic” that resulted in a number of unexpected reactions. Through a dedicated website, ISSCR gave members of the public the opportunity to signal advertisements from stem cell therapy centres and providers. ISSCR members were then given the possibility to review the latter in order to assess whether they acted under the regulatory oversight of an FDA-like authority, and if an institutional review boards was scrutinising their clinical activity from the ethical point of view. In other words, ISSCR intended to provide a public accreditation service that could have resulted in a black list of unreliable stem cell clinics appearing on their website.

Just a few months after the launch of the initiative, in February 2011, ISSCR had to discontinue the project due to the sudden reaction of clinics lawyers.

Nature, like other journals, reported on the issue. Among other things, the report affirmed that, as a result of the decision to quit the ISSCR initiative, some researchers were now worried of patients seeking for guidance at ICMS. Then the article, in an effort at giving substance to such worries, recalled the links between ICMS and Dr. Centeno's Regenerative Sciences.

Once again, on the website of *Nature*, comments appeared to the news report about this story. Notably, the first one was from Dr. Centeno. The latter wanted to decouple his name from the ISSCR story, but indeed took the occasion to make his point again on FDA's regulatory paternalism. In his comment, Dr. Centeno claimed that issue at stake was "whether one set of physicians practicing medicine using body parts (stem cells) should be held to different standards when compared to other physicians practicing medicine using body parts (for example cultured human eggs)" (Cyranoski 2011). This statement clearly refuses to conceive of stem cells as drugs only because they have a medical purpose. Thus the analogy with IVF serves the aim of showing that there exist already medical practices whereby human tissues are used without being considered drugs. The post goes on asking "why are the body parts called "stem cells" classified as a drug? Well since FDA classifies them as a drug, they must be produced in a drug factory and not a medical clinic" (*ibidem*, ref. 24692). The answer to this question clearly points, again, at purported *liaisons* between drug companies and FDA, and uses classificatory issues to unveil these alleged conflicts of interest. It thus appeared that his intention was to defend its territory from the derogatory tone of the journal's report against Regenerative Sciences.

Other comments however, provide further evidence of the existence of regulatory paternalism in the intuitions of stem cell patients and clinical subjects. Here is a list of relevant statements extracted by the posted comments that make the case for the

presence of adversarial attitudes towards what comes to be perceived as unjustified governmental and scientific interference.

> "From the layman's perspective (which I am) I want the use of my own body parts, to be of my choice and under my ownership, that includes: blood, blood transfusions, collection of eggs for fertilization, my stem cells, my skin and all of my body belongs to me, not the FDA" (24696);

> "I think that the ISSCR vastly underestimates the ability of patients to figure things out for themselves. […] After all, why should it only be the lawyers and medical researchers that have a say? Many patients also have relevant experience/knowledge – and they tend to be under-represented in the decision making" (24885);

> "At issue here is the "right" of each individual to choose the type of therapy she/he wants to follow. As a physician I have certainly seen many patients who "choose" not to follow the accepted therapies of chemo/radiotherapy […]. Like you, I have the right to live my life the way I want to: not the way FDA/NIH/Government agencies decide what is good for me" (25065).

These statements articulate a non-scholarly idea of therapeutic freedom, one that is specified against a tendency towards regulatory paternalism attributed to both FDA and ISSCR[16].

[16] Here is a list of additional comments that stress this point further:
"[P]atients are frustrated by the endless research that has so far produced little in therapies for patients at the cost of billions of dollars, much of it from taxpayers" (24696);
"I myself am a cancer survivor and I am shocked at what the FDA is attempting to do along with pharma driven anti-stem cell organizations" (*idem*);

More generally, the idea that medical information could be handled directly by the individual patient bypassing the traditional intermediation of medical communities and regulatory bodies – thus starting to act like a costumer-consumer on the free market of health-related goods – is gaining prominence in other fields of innovative biomedicine as well. This phenomenon is emerging, for example, in the field of direct-to-consumer genetic testing, and is thought to be fostered by the presence of user-friendly computing interfaces like Google. Imagining a future when complete genetic sequences will be available at affordable prices, Craig Venter (chief executive officer of Celera Genomics) said in 2005 that it will be up to the single user to find out over the Internet about the medical significance of specific variations in his genes. In the words of Venter:

> «instead of having a few elitist scientists doing this and dictating to the world what it means [to bear a certain genetic cariation], with Google it would be creating several million sicentists»[17].

These words resonate with the constitution of regulatory paternalism as a substantial obstacle to the therapeutic freedom of individuals who conceive health as a good they are entitled to buy directly from an unmediated and anonymous global market. In this vision, the patient constructs its health as a private space that he/she freely shapes and determines by resorting to innovative technologies whose fruition he/she directly controls.

"The FDA has no jurisdiction to dictate what therapies are "allowable" since they have such pathetic record of maintaining high level of food and drug standards" (24703);
"The FDA is not about successful treatments of diseases but rather a profit producer for drug companies" (*idem*);
"The ISSCR is interested in research dollars and patents. It is all about the money" (24704);
"I for one want to be allowed to make my own choices, especially regarding the right to use my own stem cells to treat myself without the ISSCR or the FDA being a roadblock in the process" (24712);
"[FDA] is one agency that would benefit from significant budget cuts" (24906);

[17] Quoted in (Nowotny and Testa 2011, 46).

Such narrative, I will show in the next section, proved strong enough to play a role in articulating ICMS' vision and political identity as an actor in the debate on stem cell translation.

4.2.2 Autologous certification

We have seen how efforts at patrolling the epistemic and normative borders of stem cell clinical research gave way to the emergence of an adversarial counter-narrative rooted in different framings of the innovation trajectory of stem cell science.

It is indeed notable that such phenomenon came to be backed by analogous efforts to set up guidance for stem cell clinical practice that looked more favourable to cellular treatments. The already mentioned ICMS guidelines (see previous chapter) articulate a set of alternative normative and technical framings of the problems of clinical translation that I will now review in some detail.

Guidance documents were adopted by the ICMS as early as 2009, just a few months after the ISSCR had issued its own. Activity of this sort, as I argued in the previous chapter, configures a kind of self-governance initiative that is typical of early stem cell translation and that is favoured by the lack of unitary legislation on those matters, as well as by the persistence of deep regulatory and technical uncertainties over the nature and the fate of stem cell innovation.

Currently, the ICMS guidelines are in the midst of a revision process. The first chunk of guidance documents, already approved in 2009, became part of a larger set of guidelines that comprise new drafts awaiting members comment and endorsement at the next Annual Congress for Regenerative and Cellular Medicine, to be held in Hollywood, FL on May the 3rd 2012. Altogether, the guidance documents, including both drafted and

approved sections, forms a total of ten separate but integrated guidelines that is worth analysing further.

The first striking feature of the guidance documents prepared by the ICMS is the explicit endorsement of therapeutic freedom. This is formulated in claims affirming that "an informed patient has the right to access innovative therapies", or that "[i]n consultation with a qualified physician, a patient must be empowered to make an informed healthcare decision" (ICMS 2009, draft section I, point 2, and draft section III, 1). The patient-doctor relationship is thus framed as an exclusive one, whereby undue regulatory interference is, in principle, unjustified. With this preliminary normative endorsement, ICMS frames its position with respect to the will of patient-consumers of stem cell therapies. The dichotomy that is being exploited here is the one between protection and empowerment. In favouring the latter, ICMS refers to narratives of denied citizenship and advocates the consumer-like rationality of patients vis-à-vis therapeutic choice. Resonant with the kind of agency, and related rights, that are typically employed in the context of commercial transactions, is the plea for transparency with respect to the estimated costs of the stem cell therapy (*ivi*, draft section III, point 2). This way of articulating the normative context of stem cell therapy, based on the alleged choice-rationality of patients, not only asserts an ethical outlook of patients' stakes, interests and capacities, but also underlies the epistemic resources that the guidelines deploy throughout, by substantially setting aside issues of protection.

As to the nature of the interventions that ICMS guidance wants to regulate, autologous adult stem cell (A-ASC as they term them) transplants of minimally manipulated cells are the sole concern of these documents. The amount of manipulation is quantified as minimal if cell culture lasted less than ten passages after colony formation and did not exceed the limit of sixty days (ICMS 2009 adopted section VII, page 6). These

limits supposedly assure that potentially risky genetic alterations of the cultured cells do not occur. Obviously, however, these limits are arbitrary, both in regulatory and scientific terms. Nevertheless they serve the fundamental function of somehow preventing FDA claims to control the procedure. Again, co-production is manifest, as the technical requirements for preventing incontrollable genetic mutation performs a clear regulatory function. The medical practice/drug divide, far from being a pre-given ontological distinction, is worked out, at the same time, as a technical and regulatory parameter to prevent governmental oversight and assure safe transplants. That it is the intention of the ICMS to avoid dealings with FDA and the Department of Health, thus appears in full clarity when the guidelines state: "The use of autologous, adult stem cells is the practice of medicine and, as such, is subject to the laws and regulations that cover the practice of medicine" (ICMS, 2009, draft section I, point 1). To the very same aim, the already mentioned reference to cultured embryos for IVF treatment plays the role of stressing the medical practice-character of A-ASC therapies. IVF, according to 2009 approved Section VII of the ICMS guidance documents, transited from a "simple tissue transplant procedure to a cell culture technique" (*ivi* page 1) to allow screening of embryos suitable for implantation. Nevertheless, so the argument goes, IVF continued to be considered as a "practice of medicine and not the production of a biologic drug" (*ivi*, 2). This last remark is evidently unnecessary here, if not to exactly make a point against interventions like the 2008 FDA injunction that I reported above. Once again, a conceptual argument drawing on ontological similarity between IVF-related embryo culture and in vitro expansion of adult stem cells is used to mark the territory from undesired political intrusions.

The imaginary that ICMS is advancing, here, includes implicit assumptions on the consumer-like agency of patients in an attempt to normalise the use of unproven stem

cell therapies. The credited epistemic values of clinical research are downplayed in the name of therapeutic freedom.

Among the most innovative features of the entire edifice constructed by these guidelines is what ICMS calls the 'clinical staging' for cell lines to be used in medical practice. In a not too hidden effort of mimicking the epistemic structure of stepwise CCTs, clinical staging sets standards by which cell must abide in order to be used in difference kinds of clinical practice.

Clinical staging is a classification of cell lines according to the previous clinical and pre-clinical applications they were used for. According to the clinical staging classification, an increasing number of patients and an increasing length of monitoring confer a cell line liability to further and further less restricted uses.

For the sake of illustration, it will be convenient to report the entire paragraph on clinical staging below and let my comments follow. The phases of ICMS clinical staging for cell lines are so described (ICMS 2009, adopted section VII):

> «*Pre-Investigational Cell Line* (PICL): No animal data is available. These cell lines should not be used in humans until animal data is available.
>
> «*Early Investigational Cell Line* (EICL): This is an un-established stem cell line being used in a new tissue where several animal models exist that show efficacy and safety, but no human data exists. An un-established cell line can be used in early stage human studies where 5-10 patients are treated and followed for a minimum of 6 months. The physician should be able to document subjective and objective outcome measures. Once these criteria are met and no significant complications have been reported, the

cell line moves to the next grade. Note that before LICL patients can be treated, a minimum of 6 months follow-up is required at EICL.

«*Late Investigational Cell Line* (LICL): This is an un-established stem cell line being used in a new tissue and is being tested in humans in larger numbers, typically 20-50 patients who are followed for a minimum of 6 months. The physician should be able to document subjective and objective outcome measures. Once these LICL criteria are met and no significant complications have been reported, the cell line moves to the next grade. To move onto treating ECCL patients, at least 20 of the LICL patients should be at the 6 month follow- up stage and have no complications.

«*Early Clinical Cell Line* (ECCL): This is an un-established stem cell line being used in a new tissue and is being used for early stage clinical treatments in 50- 200 patients that are followed for a minimum of 6 months. The physician should be able to document subjective and objective outcome measures. Once these criteria are met and no significant complications have been reported, the cell line moves to the next stage. To move on to treating LCCL patients, at least 50 of the EICL patients should be at the 6 month follow-up stage and have no complications.

«*Late Clinical Cell Line* (LCCL): This is an un-established stem cell line being used in a new tissue and is being used for early stage clinical treatments in 100- 300 patients that are followed for a minimum of 6 months. The physician should be able to document subjective and objective outcome measures. Once these criteria are met and no significant complications have been reported, the

> cell line moves to the next stage. To move on to treating CG patients, all phases of the staging must be completed.
>
> «*Clinical Grade* (CG): This is an established cell line that has completed all stages above and is being used in patients in an unrestricted fashion. All patients being treated must still be entered into the ICMS Re-implantation Registry».

The ICMS Re-implantation Registry is a database devised and maintained by ICMS that aims at collecting information about safety and efficacy of A-ASC re-implant procedures. It should shortly be supported or integrated with a Treatment Registry where patient and clinician testimonies are collected. This kind of information is obtained on a voluntary basis from patients who receive treatments and clinicians who perform them, with the overall aim of providing the A-ASC user community with observational information on the clinical characteristics of cellular therapies. Moreover, the registry also works as a cell bank. For each submitted safety and efficacy report, ten cell samples from the same patient (presumably in the form of frozen vials) and two resulting from two culture expansions from the same patient, are stored at the Registry. The idea here is to back-up cell samples to analyse in the case of future complications or adverse reactions.

A first point to mention here is that, being clinical staging about autologous stem cells, it is not possible to understand the expression 'cell line' in terms of direct lineage with a clonal ancestry. Since every patient receives a newly established cell line, it is more correct to speak of cell types rather than cell lines. The same cell type batches from different patients do not constitute a cell line in any lineage-related sense of the word. The language here is, I believe, intentionally misleading and not simply sloppy. Speaking

of cell lines conveys the idea that all cells belonging to the same "line" behave similarly, which would confer some more biological consistency to the clinical staging categories. Obviously, however, cells of the same tissue type, but not of the same patient, can hardly be thought as having the same genetic make-up and phenotypic behaviors, given biological variability between individuals and tissues of origin and age, to say the least. The burden of proving that the same cell type will act in the same manner in autologous re-implantation procedures in different patients is on the shoulder of practitioners, and is a matter of statistical inference no less than is in the case of heterologous cell therapies with a *bona fide* clonal cell line, or new drugs. Simply assuming, like ICMS does, that, a 'cell line', that is to say, cells of the same tissue, will have similar safety and efficacy profiles in different patients is unproven, and represents a clear departure form EBM standards of inference. In other terms, clinical staging, albeit mimicking the stepwise process of CCTs, establishes safety and efficacy standards in an unrigorous way. To begin with, safety and efficacy profiles for 'cell lines' are established in the context of medical practice, and not in properly designed and controlled experiments of clinical research. This feature contradicts a dogma of modern medicine according to which doctors shall not try to gain knowledge from experimental medical procedures, nor shall they have research subjects believe that they will get any benefit for themselves from participating in randomized, double-blind clinical research trials. This is not to deny that many current standard-of-care procedures were established in the past from experimental practice and not from CCTs. Examples of this sort are organ transplantations, BM grafts and IVF treatments – to which latter ICMS frequently refers to as a telling precedent. It has however been the case that those procedures have been the object of later systematic and independent meta-analysis studies through which their safety and efficacy have been established, to the best of our current epistemic standards. The ICMS clinical staging,

instead, coupled with the Re-implantation Registry, marks a big step outside the pathway of EBM. These tools work as a clearing house for the use of cell types in autologous stem cell transplant, but lack any decent display of accepted criteria for sound medical inference.

The reason why a cell type so far only tested on animals, can be authorized to be used in humans provided in small numbers thereof, like the guidelines say of EICLs, is mysterious. The guidelines omit to specify which kind of tests, of which kind of cells, on which kind of animals provide sufficient evidence of which kind, about the safety of going in humans with those cells. Similarly, why should one be convinced that "subjective and objective measures" produced by an involved clinician can constitute sufficient ground for another clinician to undertake analogous procedures? Or again, what is the rationale for assuming that simply enlarging the involved cohorts – without establishing any credible negative control, nor any positive control with existing standards of care – can produce statistically valid inferences about safety and efficacy?

What is worth noticing here, in this clumsy exercise of standardisation, is the tentative establishment of a whole set of different parameters for the acquisition of clinical knowledge. The Re-implantation registry is a way for ICMS to gain authority and control over the activity of stem cell clinics, thus severing blatantly mischievous practices from allegedly credible ones. This exercise of appropriation relies on the mutually reinforcing construction of unconventional clinical criteria and alternative normative commitments.

Commenting on the establishment of the Registry, ICMS director David Audley said to *Nature Medicine*:

> "The most important thing is to put the information out there so that *patients and clinicians* can look at it and make their own conclusions […]. We're not making recommendations on any one of these clinics [emphasis added].
>
> This is just the data that you as a consumer or a clinician need to look at" (cited in Dolgin 2010).

The inspiration that guide ICMS could not be stated in clearer terms. Prompted by ideas of therapeutic freedom and refusal of regulatory paternalism, ICMS tries to build up a new system of clinical knowledge validation, in veiled polemic with ISSCR "Submit a Clinic" initiative (see *supra*). The most unorthodox feature of the former is its refusal to acknowledge any authority and constraining power to the most cherished validation tool of the science of our time: peer-reviewing. Nowhere in the guidelines any reference is made to the legitimating epistemic role of the scientific community as a source of knowledge validation. In a typical display of a co-productive dynamics, ICMS takes upon itself the authority to set criteria of scientific validity and, in so doing, states again the inappropriateness of intrusions in the therapeutic choices people and physicians. This last feature is evident in the framing of the patient as a consumer, one who has an exclusive relationship with doctor, conceived as the provider of medical services.

ICMS, with these guidelines, is fencing off the territory of therapeutic freedom from the unduly interference of both the state and the official scientific community and it does so by elaborating of *ad hoc* new standards of scientific validity.

In draft Section IV of the guidance documents, ICMS says that "[a]ny data should be validated by an independent, third party organisation prior publication of any claim of safety or outcome"(ICMS 2009, draft section IV). Soon after however, it is also said that

"[w]henever possible, patient data should be collected and managed in Treatment Registry" (*ibidem*). This is tantamount as saying that it is ICMS here that performs the function of the independent third party.

The scientific community is thus not seen as a partner in the validation of scientific claims, but rather, let us recall it here, as an unreliable interested party in the commercial venture towards stem cell innovation. Accused of ties with the industry, and bonding with FDA in slowing down the pace of new therapies, the official scientific community is denied the very essence of its function as a validating source of expertise through peer-reviewing.

A further remarkable feature of the ICMS guidelines is the definition of Minimal Risk and More than Minimal Risk Categories. In a clear effort at framing A-ASC interventions as bearing only minimal risks, the guidelines attempt an unprecedented classification of human tissue of origin. According to the latter classification, tissue type-groups exist that lump together tissues of different kind. The idea behind this classificatory effort is to link new tissue type-groups to a ready-made risk assessment criterion: cell transplant occurring within the same tissue type-group bear only minimal risk, whereas attempting to transplant a cell type that belongs to a group into a bodily site that belongs to another implies more than minimal risks. The proposed tissue type classification is articulated as follows (taken from ICMS, approved Section VII, page 15-6):

- Ectodermal Integument: Skin (epidermis), hair, nails, sweat glands, teeth enamel, inner ear, eye lens

- Ectodermal Upper/Lower Digestive Tract: Mouth, Pharynx, Terminal Rectum

- Ectodermal Neurological: Peripheral Nervous System, Central Nervous System, Autonomic Nervous System, Retina, Pineal Body, Posterior Pituitary, Cranial and Sensory Ganglia

- Mesodermal Vascular: Heart, Vascular Smooth Muscle, Artery, Vein

- Mesodermal Orthopedic: Muscle, Tendon, Cartilage, Bone, Ligament, Intervertebral Disc

- Mesodermal Organ: Spleen, Kidney, Adrenal Glands

- Mesodermal Integument: Skin (Dermis)

- Mesodermal Urogenital: Oviducts, Uterus, Epididymis

- Endodermal Organ: Endocrine-Pancreas, Thyroid

- Endodermal Organ: Digestive-Liver

- Endodermal Respiratory: Trachea, Bronchi, Alveoli of Lungs

- Endodermal Urinary: Bladder-Urethra

- Endodermal Digestive Tract: Esophagus, Stomach, Small Intestine, Colon

Again, like in the case of clinical staging, it is possible to appreciate here the mutually productive relationship between scientific categories and normative parameters relating to risk. Classification criteria, far from reflecting immutable attributes of naturally

occurring phenomena, are mobilized to accommodate favorable risk assessment. The boundaries between bodily parts are functionally rearranged in a way that fits assumptions about safety of practising stem cell therapists. This is indeed a creative effort to project scientific credibility onto cellular transplantation, and to provide risk categories with the advantage of corresponding to physiological ones. Of course, the latter are a sheer construction, and there is nothing "natural" about them. Nevertheless, epistemic and value-laden judgments are here closely knitted together to bring order and exert control on the practice of cell treatments.

This case is a clear illustration of how the co-productive lens can bring the mutual relation of epistemic and normative instances into relief. Other theoretical frameworks are not as sensitive in reconstructing how knowledge and values are mobilised by actors involved in a science-related controversy or litigation.

4.2.3 Banking cells and risk control

A similar, although less comprehensive and unorthodox effort at gaining control over human cellular entities through classification is the UKSCB distinction between 'research grade' and 'clinical grade' human cells. Just like ICMS, the UKSCB sees itself and tries to establish itself as a certificatory agency. Based on claims of scientific expertise, the UKSCB can lay claims as to the appropriateness of doing clinical research with human subjects using this or that particular cell line. The UKSCB grading system imports good manufacturing standards into the classification of research grade and clinical grade human cell lines. In so doing it frames the risks associated with first-in-human clinical research in merely technical terms. This move normalizes stem cell clinical research by limiting the width of factors that bear on the construction of risk categories. Once a cell line has received clinical grade classification, the research group that is willing to use it

obtains, so to say, a green light to go ahead with its clinical studies. Such an authorization is based on both scientific and ethical assessment of the distributed cells. As I have already mentioned, not only clinical grade stem cells have to pass GMP testing, they also have to show their derivation was completed in compliance with internationally accepted standards of tissue donor informed consent. This projects a good deal of credibility on the certification and distribution activity of the UKSCB and, by the same token, gives scientific groups sufficient confidence that, in some important respects, their activity with UKSCB cells is socially acceptable. No other factors, other than strict compliance with EU standards of GMP, including donor consent, are conceived as having importance in the initial decision to distribute a cell line to clinical researchers. Further regulatory oversight on stem cell clinical research will be delegated to agencies such as FDA, MHRA, or EMA, depending on the geographical location of the team that uses UKSCB lines. But the risks connected to human tissue circulation in stem cell research are framed as being technically manageable, centrally controllable and scientifically affordable.

Thus, banking of human cell lines in the UKSCB establishes both a scientific and a normative order through attested expert certification and dedicated classification. The UKSCB thus attains prominence as an international hub of human tissue analysis, storage and distribution.

I have already described in the previous chapter how this classification corresponds to the UKSCB adoption of an open source model of human cell circulation. However, now that the first stem cell lines are receiving clinical grade approval (Department of Business Innovation & Skills, Department of Health, UK 2011), this cooperation-oriented framing of the field's efforts in research and innovation are being

contested. One evident pitfall of this model is that commercially oriented actors seeking to exploit proprietary technologies are likely to be damaged from sharing practices, thus ultimately having to refrain from depositing their cell lines. Furthermore, it has been argued that holders of IP rights on a given cell line, is likely to face reputational risks in an open source model (Courtney *et al.* 2011). Reputational risk has to do with possibility of two research groups (or more, for that matters) using the same cell line in two distinct translational projects. Given difference in handling and cell culture conditions, the same cell line might end up behaving in different ways in different clinical contexts. If the cell line experiences adverse effects in the hands of one group, so the argument goes, "regulators are likely to question [its] fitness" for the other group as well (*ivi*). This, at the very least, is bound to increase the developmental costs for the latter group – both in terms of money and in terms of time. Thus in this case, the UKSCB framing is criticized on the basis of its potential to undermine research and slow down innovation.

Compared to the framing of clinical staging that I described in the previous section, the classification used by UKSCB appears to be more in tune with the standards, epistemic and ethical, of the official scientific community. UKSCB, moreover, is endowed with a much higher degree of credibility then ICMS, provided by its institutional affiliation with the Medical Research Council (MRC), and by its scientifically prestigious steering committee. However, it cannot go unnoticed that, albeit epistemically weaker and of lesser academic reputation, also ICMS rewiring of clinical staging and tissue type classification are "materially powerful" (Macnaghten, Kearnes, and Wynne 2005, 12) tools for structuring ICMS power claims as a certification authority and a clearing house for stem cell clinics. It is thus crucial to understand while interpreting conflicting trajectories of biomedical innovation, that the involved actors, irrespective of their scientific standing,

strategically try to position themselves by advancing their epistemic and normative visions in a mutually reinforcing fashion.

I have shown that, as soon as we scrape against the surface of this issue and stop taking for granted distinctions between certified/uncertified science, proven/unproven treatment, responsible/self-interested practice, research subject/patient, expert/layman we found divergent values, visions and commitments struggling for supremacy. This speaks of the great uncertainty, both normative and technical, that surrounds stem cell medicine. In such a context, the meaning of those distinctions does not come pre-boxed in an uncontroversial form. Rather, those meanings are re-stated, contested, re-worked out, negotiated, defended and ultimately used to mark spaces of action and to define identities.

I will now turn my attention to the mobilisation of resources that actors resort to in the practice of state-regulated stem cell controlled clinical trials (CCTs).

4.3 Clinical trials and affordable errors

In this section I will introduce the role of controlled clinical trials (CCTs) as a resource to exert control over the transactions that, like those described so far, are happening at the junction between stem cell research and their clinical application (4.3.1). Furthermore, in section 4.3.2, I will describe the shared model of governance in the case of publicly regulated clinical trials as characterised by a specific version of what Latour and Woolgar called the 'credibility cycle' (Latour and Woolgar 1979, ch 5).

4.3.1 The disciplining role of CCTs

In order to make sense of the conflicts arising around different models of clinical translation, it is now of some importance to succinctly appreciate the purposes of controlled clinical trials, as they are intended by the international medical community. To begin with, the aim of a CCT is not, in any of its stepwise phases, to attain treatment for the research subjects. The possibility of a given medical product to be effective for the patient in the research context cannot be ruled out, but the real aim of a CCT is to gain scientifically sound knowledge on the effects of the tested product on the target population. Clinical trials thus aim at two interconnected gains: first, to test safety and efficacy on the research cohort, and second, to attain statistically reliable grounds for thinking that the treatment will have similar effects and side-effects in the general population to which it is targeted. To these aims the number of participants increases as the trial proceeds to its more advanced phases, so as to gain statistically relevant data on the tested product. In this sense, CCTs are a genuine research tool and not a therapeutic setting, meaning that they point at gaining knowledge and not at curing people. Attempting an innovative medical procedure on a patient, might well contribute to the gain of knowledge, but one that lacks the generalizable character of CCTs. There are indeed examples in the history of medicine showing that innovative medical procedures eventually resulted in fully established therapeutic paradigms. But the medical procedure itself, in those cases, did not do anything more than providing a proof-of-concept that, it is assumed, should finally be validated by means of a CCT. Nowadays, there exist widespread consensus on the idea that trying to establish proof-of-concept for a new treatment on humans without previous pre-clinical data speaking in favour of it, is a risky shorthand for establishing scientifically sound conclusions and, for this reason, it is

ethically unacceptable to proceed with research on human subjects without prior extensive characterisation in non-human models.

Moreover, when the necessities of clinical research lead scientists to enrol unhealthy volunteers in a clinical trial, every effort must be made to avoid therapeutic misconception. Along the same lines, when due to the exhaustion of available therapeutic means, a medical doctor resorts to experiment a new procedure or an off-label prescription, strictly defined conditions must hold: first, that the patient does not have further reasonable chances of resolving her condition; second, that the patients and her relative understand the risks the procedure involves; and finally that the outcome of the procedure is made public to the scientific community.

Speaking of publicity, regulated clinical research does not mandate the publication of preliminary results in peer-review journals. Nevertheless, as opposed to the kind of experimental procedures of the last section, the public dissemination of information about on-going trials through peer-review and disclosure to regulatory agencies are generally assumed as hallmarks of correctness and commitment to the public aims of scientific research.

Notwithstanding international consensus on those general principles of clinical research, CCTs have been, and indeed continue to be, occasions of major disagreements within the scientific community and in regulatory agencies. This point has not received all the attention it deserves in the literature about the ethical and sociological dimensions of clinical research. Most scholars are perfectly aware of the fact that disagreement on trial design, execution and oversight keep on recurring, especially in innovative areas of clinical science. Nevertheless, recurrent failures of this cherished paradigm in creating stable regulatory conditions for innovative clinical research have rarely, in my opinion,

been fully thematised and discussed. Even within strictly defined ethical boundaries and agreed upon epistemic criteria, staged clinical research often proved sub-optimal in absorbing disagreements within the clinical community and in generating enduring public trust within larger publics. This is not to say that the ethical and scientific principles guiding development of new drugs or new therapies are inherently inadequate to do their job. Nor my remarks have to be taken as implying that tighter and more precise regulations, guidelines and oversight mechanism are desirable. It is however a fact that, despite the high level of scientific agreement on the general principles of clinical research, scientists, ever more often, find themselves on opposing sides of harsh debates about innovative therapies and the occurrence of adverse events.

Gene transfer research offers a vivid example to illustrate how the institutionalised management of risks and uncertainties, *de facto*, may fail to protect both clinical science and clinical research subjects in the case of innovative therapies – as testified in the following famous case.

Ornithine Transcarbamylase Deficiency (OTD) is a recessive genetic disease caused by the incapacity of the liver to control the production of an enzyme that is crucial in the metabolism of ammonia. People affected by OTD present excessive levels of ammonium ion in the brain, a condition that leads to brain damages such as encephalopathy. In its more acute manifestations, OTC is conducive to death during infancy. The standard of care for acute OCT is liver transplant. For milder manifestations of the disease however, the genetic underpinning of OTC suggests that correcting the genetic defect responsible for the metabolic disorder, may be a promising therapeutic strategy. In 1999, Pennsylvania University researchers Steven Raper and James Wilson, founder of Genovo Co., thus initiated a clinical trial to test the safety and efficacy of a gene transfer protocol to treat mild forms of OTC (Batshaw *et al.* 1999). Scholars in the field of research ethics

know all too well what happened in the course of this study. On 13 September 1999 an eighteen year-old patient named Jesse Gelsinger received a recombinant vector injection in his liver. Seventeen people had received the vector before Jesse, and none had been reported to experience major complications. A few ours after the procedure, however, Jesse began to hyperventilate and fell into a coma. He eventually died four days after receiving the vector (Emanuel 2008, ch 10; Kimmelman 2010, ch 3). Less than three years after the event, the Institute for Human Gene Therapy at the University of Pennsylvania, chaired by Wilson himself, was shut down.

The Gelsinger case soon became the subject of ethical and medical discussions and rose to the level of a textbook example of what can go wrong in clinical research. After the Gelsinger incident, commentators argued that a number of factors impinged negatively on this unfortunate outcome. In particular, it has been argued that the medical *équipe* did not fully respect the protocol in the case of Jesse[18]. Furthermore, some have argued that the team leaders were known to be very ambitious scientists and that pressure from the industry may have been particularly strong in those time – which might explain a "cavalier" attitude towards generating clinically relevant data (Kimmelman 2010, 34). Also to this point, during the proceedings of Jesse's father lawsuit against the University of Pennsylvania, it emerged that individual and financial interests were not properly disclosed to participants in many occasions.

Although a full account of the intricate story of the OCD trial is beyond the scope of this dissertation, two considerations are nevertheless in order here. First, Gelsinger's death brought the credibility of gene transfer clinical research to a sudden drop. A line of

[18] In particular an FDA audit revealed that Jesse's blood ammonia levels were good at the moment of recruitment but exceeded exclusion levels at the moment of dosing – thus requiring the research team to exclude Jesse from the trial. It has also to be noticed, however, that such diversion from the established protocols was approved by FDA itself.

research that was considered the most promising fruit of the biotechnological revolution initiated with recombinant DNA experiments in the early Seventies, abruptly came to be seen as harbouring more risks than promises, and gene therapy soon started to epitomise the delusion of a broken medical dream.

Secondly, it has to be recalled that the intensity of regulatory oversight that attended to the accomplishment of the OTD gene transfer clinical trials was unprecedented. In striking contrast with the absence of detailed public dispensations in the field of innovative stem cell medicine (see supra chapter 3.II), the NIH had issued extremely accurate "Guidelines for Research Involving Recombinant DNA Molecules" in 1994 and had kept on amending and updating them regularly. NIH Recombinant DNA Advisory Committee, originally established in 1974, directly revised the clinical protocol proposed by Wilson and colleagues according to NIH Guidelines before starting recruitment in 1997. FDA was obviously overseeing the trial as well, and NIH had established an Office of Biotechnology Activities (OBA) with the intent of making all information about r-DNA activities available to the FDA and to the public as well. All these safeguards notwithstanding, what strikes as surprising is not so much Jesse's death in itself: although unfortunate, severe adverse events can occur in clinical research. it is indeed remarkable that a huge display of regulatory oversight eventually proved insufficient to prevent a casualty that ended up undermining the credibility of an entire field of biomedical innovation.

Therefore, if a lesson can be learnt form the OTD case, it is that not necessarily a system of closer regulatory oversight than the one that is in place for stem cell translation is conducive to more efficient governance of biomedical innovation.

In the present shared model of governance for stem cell innovation, many blind spots remain as to how clinical and ethical criteria will be negotiated between practitioners and regulatory bodies. This is especially true of the arguably most innovative and uncertain area of application of stem cell clinical research, that is to say, first-in-human research with human embryonic stem cells and their derivatives.

As yet, only a few companies are on their way to start, or have just initiated clinical trials with stem cell of human embryonic origin. Currently, four major clinical trials with innovative stem cell approaches are underway.

Geron Co., the unique licensee of the WARF patents on human embryonic stem cells, is currently performing phase I for spinal cord injury in selected centres throughout the States[19].

Advanced Cell Technology has two FDA approved phase I/II clinical trials, one for dry age related macular degeneration, and one for Stargardt's muscular dystrophy, both involving derivatives of embryonic stem cells.

ReNeuron, a company based in the UK, has recently gained clearance to initiate the first approved clinical trial – called PISCES – for treating the aftermath of stroke with foetal neural stem cells. They are planning to use their *CTX* cell line in a clinical protocol called ReN001. In their website, ReNeuron explains that CTX cells are obtained through

[19] On November 14th, 2011 Geron Co. decided to discontinue all its stem cell-related programmes, including the CIRM-sponsored Phase I clinical trial on spinal cord injury. Unfortunately, being this episode so recent, I could not give full account of it in this dissertation. Being Geron among the most important and innovative companies in the stem cell field, a brief comment is however necessary. Geron press release indicates that among the causes of this decision the present global financial crisis might have played a role. In particular, the company refers "capital scarcity and uncertain economic conditions" as motivations behind its decision (see Geron website). Furthermore, they also make reference to "clinical, manufacturing and regualtory complexities" as reasons for discarding stem cell programmes (*ibidem*). This decision, in my opinion, may have profound implications for the whole field in terms of credibility and ability to purge funding from venture capital firms and from the stock market. Obviously, further research into the causes and consequences of this important industrial decision will be decisive to assess its impact.

proprietary cell expansion and cell selection technologies and that they qualify as commercial-grade cell therapy products that would match all possible patients. Additionally, ReNeuron is developing a stem cell-based treatment for blindness (ReN003) and another one for peripheral arterial disease (ReN009).

Furthermore, Viacyte, formerly known as Novocell, is bound to file an Innovative New Drug (IND) application to the FDA for a phase I clinical trial with Pro-Islet™, a stem cell line of embryonic origin that, in the intention of the company, may replace intensive insulin therapy for diabetic patients. The company is currently performing pre-clinical studies to support the FDA application with convincing evidence of safety and proof-of-concept efficacy.

These four companies are uniquely positioned as the initiators of the translational phase of stem cell innovation within the boundaries of state-regulated CCTs.

It is however too early to have a picture of how the relationship between researchers, regulators and the public will be developed and articulated[20]. For this reason, it is also not possible to fully anticipate how scientists in research groups and their colleagues in regulatory agencies will cope with each other. By the same token, considerations about public reactions to possible adverse events in this field of clinical innovation are bound to remain speculative.

One observation is nevertheless possible. What is emerging, is that scientists both at the clinical and the regulatory side are bound to use pre-clinical studies and early data form the first research subjects to articulate their respective narratives on safety and efficacy. Notions of risk will be negotiated with ideas of epistemic credibility, and

[20] A thorough comparative examination of these cases will be the object of a EU-funded research project led by Prof. Brian Salter (King's College London), Dr. Alex Faulkner (King's College London), Giuseppe Testa (SEMM – IEO) and me in collaboration with the Bio-objects research consortium (link).

eventually balanced with considerations relative to public acceptability of safety standards. However, the public itself seems unlikely to be granted the opportunity to voice its own concerns and, even less, to participate in the construction of this incipient trajectory of innovation.

4.3.2 The stem cell credibility cycle

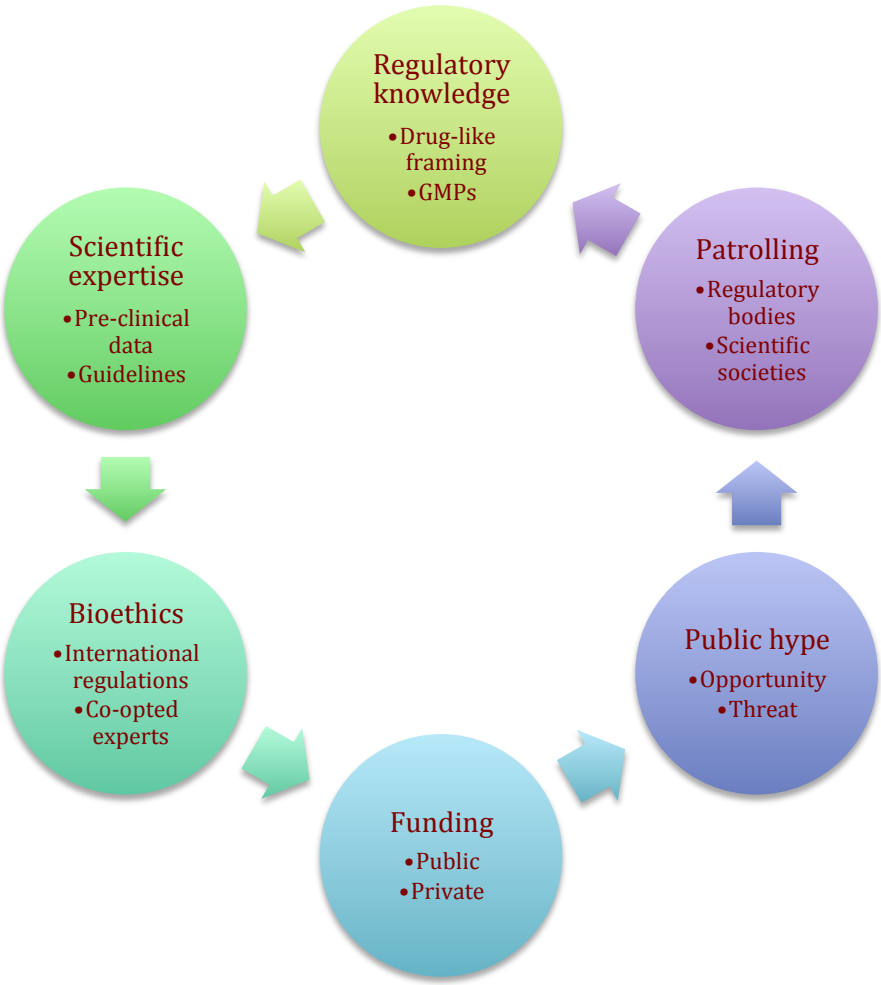
As I said above, according to the shared governance framework a network of diverse actors is taking position around the development of stem cell clinical research. this network constitutes what has been described as a 'credibility cycle' (Latour and Woolgar 1979, 201). According to this explanatory framework, it is possible to track the array of actors, activities and tools that converge to provide internal as well as external credibility to the scientific enterprise In general terms. Credibility cycle analysis is thus able to visualise how the production and certification of scientific knowledge is subject to a wide array of influencing factors. More specifically, credibility cycles explain how public trust, scientific knowledge and economic resources are mutually transformed into one-another to make the pursuit of professional objectives possible. Typically, credibility cycles depict the interplay of mechanisms to attain power, claim professional capacity, demonstrate efficacy, achieve credibility, being recognised as a credible expert, being attributed decisional status and influence and, back again to the origin of the cycle, acquire power over the governance of a social phenomenon (adapted from Fleck 1997).

The notion of credibility cycle has fruitfully been applied in science studies to a variety of social phenomena, especially in the field of scientific controversies and technological development. In particular, credibility cycle analysis proved useful to reconstruct the behaviours and explain the strategic moves of organisations, such as

research councils (Rip 1994), scientific institutions (Latour and Woolgar 1979) and the privately sponsored scientific groups (Jacob 2009).

In the case of stem cell clinical research, the credibility cycle serves the aims of creating the conditions for clinical errors to be affordable and not to ultimately impinge on the overall tenability of stem cell innovation. Thus discursive resources are mobilised – both epistemic, ethical and political – building on a number of elements that can be captured in the following diagram (Figure 1).

Figure 1: The credibility cycle



In both the US and the UK, dedicated governmental agencies frame clinical translation as being about the development of an innovative biological drug, and set standards of good manufacturing practices. The latter dispensations convey a political message of risk stabilisation and public oversight by setting technical standards to which practising scientists have to conform.

This is intended to bring under control the activity of clinical researchers that are sponsored with money, both public and, to a much greater extent, from private investment capitals. Private companies provide research with the necessary resources and reinforce the idea that stem cell innovation is economically valuable, if translation to the clinic succeeds. At the same time however, resorting to market capital requires evidence that commercial interests are not capturing the whole enterprise in epistemically and morally unacceptable ways. This is why stem cells are framed as drugs, and GMP parameters are set forth in the first place. This configuration establishes a first filter on clinically unacceptable cellular therapy, one that, it is worth recalling, practitioners agree with. At this level of the credibility cycle, regulators and scientists do not find themselves in an adversarial relationship.

As we move on into the circular direction of the diagram however, we see that GMP standards are able to stabilise only one part of the relationship between oversight and clinical research teams. The tension between commercially driven efforts and public oversight on clinical development is substantially left to an open dynamic. Scientific expertise mediates between the regulatory expectations of governmental agencies on one side, and the commercial interests of industries and researchers on the other. As to the ethical concerns that such an open-ended relationship can elicit, as I also said, they are handled by means of a principled bioethical approach. This happens, mainly, by including specialised staff in advisory bodies, scientific societies, IRBs and regulatory agencies. It is thus by building ethical expertise within the process of clinical oversight that the whole enterprise seeks to construct its ethical credibility, especially in matters of informed consent and safety provisions with respect to research subjects.

Peer-reviewed pre-clinical evidence, and adherence to the stepwise process of clinical development join a principled bioethical approach (administered by co-opted

experts and included in guidance documents) to provide confidence over the good functioning of the relationship between regulatory choices and commercially sponsored research. Contrary to the gene therapy case, regulatory agencies do not provide any detailed guidance as to how much and what specific kinds of practices and evidence should inform the shift from pre-clinical to human clinical research. The burden of certifying proof-of-concept validity and risk assessment considerations is entirely left to a self-administered process of peer-reviewing and individual communication between the research team and the regulatory bodies. Peer-reviewing and CCTs are, so to say, the common currency that allows transactions between regulators and practitioners to take place. They therefore perform an analogous function as the language and principles of canonical bioethics (Evans 2000 and 2002) in the context of divisive public issues: they stabilise the normative and the epistemic order around a common core of shared practices and values, thus projecting credibility on a specific framing of the problem of stem cell translation.

Again, scientific actors who adhere to the framing in this model – like ISSCR, for example – see peer-reviewing as a guarantee of their scientific independence and value it as the most reliable tool for knowledge certification. As I tried to explain elsewhere, however, this leaves ample room for discretionary decisions to be made. Those decisions include real-time trial design adjustments according to data and evidence that might arise in the course of clinical and pre-clinical research. Regulators and practitioners, however, converge on this relatively under-regulated mode of interaction for two reasons. First, given the high degrees of uncertainty that characterise such innovative clinical efforts, a good deal of flexibility is required to cope with them in a co-ordinated fashion. Second, and directly relating to this first point, this flexibility assures that the pace of clinical

development be adapted – either by slowing it down or by speeding it up – to the actual degree of knowledge gathered as clinical studies unroll.

So far, we can observe that the shared model of governance maps onto an agreed upon scheme of ethical and epistemic criteria. Our diagram however, introduces more problematic elements as we move to the right hand side of it. As I illustrated in chapter two, the clinical promise of stem cell research has generated almost uncontrollable levels of public hype that is reinforced, together with increasing expectations, each time a new clinical projects successfully secures new funding. Practising scientists and politicians are also partly responsible for this phenomenon, as keeping expectations high is generally conducive to secure stronger support – and budgets – for research and clinical development. To a certain extent however, public excitement about the therapeutic outcomes of an innovative field of medicine is also likely to be exploited by less than scrupulous subjects – as shown in other sections of this chapter.

It is thus to control the proliferation of hype-driven excesses that an intense patrolling activity is being enacted to exclude alternative modes of framing the pipeline of clinical development – see the ICMS controversy above. We saw that a variety of actors, often with the sincere complicity of patients, exploit different versions of the credibility cycle, by stressing elements that are not included here, such as therapeutic freedom and creative forms of cell line clinical staging.

Ultimately, and so the cycle reaches back to its inception, regulators and scientific societies try to counteract these alternative modes of clinical translation by re-stating principles of GMP and by constructing stem cell products as innovative biological drugs.

It appeared from my previous analyses that the epistemic and ethical standards of clinical research, albeit at least partially entrenched in legislation and patrolled by

dedicated agencies and scientific societies as well, fall short of forming a stable framework for translational debates to peacefully take place. Quite on the contrary, the enforcement of epistemic and ethical commitments into the institutional design of regulatory activities, constitutes an occasion for the emergence of contestations and alternative political narratives, whereby those commitments are reframed and reinterpreted.

The cases I reported in this chapter testify to the material power of alternative constructions of clinical research. The fact that they may appear scientifically unconvincing and politically misguided, as they appear to me for instance, does not but reinforce the idea that it is not on established, pre-given categories and distinctions that clinical narratives and counter-narratives rely for doing their job. And I have provided evidence, in the above sections, of the ability of stem cell stakeholders to partner up with real therapeutic interests, and viable understandings of the relationship between people, their diseases and the state. By so doing they seek control over their clinical activities and construct their image with respect to other stakeholders.

As I anticipated in the beginning of this dissertation, major rearrangements are at play at the junction of stem cell research and clinical application. Long-held ideals on how we should continue the battle of mankind against morbidity challenge the very nature of democracy in its relationship with science. The state is alternatively conceptualised as an ally or as an enemy in the individual research for healing – and the scientific community as well. The latter, just as it tries to establish shared criteria for safe and efficacious clinical innovation, comes to be perceived with suspicion. The model according to which it is experts that certify knowledge, and regulatory science that certifies experts no longer represent the backbone of credible science policy, at least when the political conditions

exist to hold a variety of differing opinions on what counts as legitimate expertise, as the cases just presented stand out to demonstrate.

FDA and ISSCR, on their part, showed a sincere commitment in the protection of stem cell patients and clinical subjects, but this did not prevent alternative visions from emerging and from giving rise to a socially relevant therapeutic phenomenon. That stem cell clinics proliferate and provide their services to patient-consumers is a matter of fact. And also as a matter of fact, ICMS succeeded in providing some stabilization to the otherwise boisterous phenomenon of stem cell therapy clinics.

Every actor in this game of demarcation is scared of loosing credibility. Obviously ISSCR does not want to play the part of an industry-driven obstacle to stem cell innovation. Along the same lines, ICMS shows a strong interest in depicting its activities, and those of its members, as legitimate and reliable. To these ends the ISSCR lines up with the FDA, of which it shares the epistemic and normative premises, and tries what it can to contrast the emergence of unproven stem cell treatments. On the other pole of the divide, ICMS interprets the existing regulatory regime in its favour and exploits a globalised world to circumvent it. The displacement of stem cell therapy across national borders is indeed a major feature of some of the phenomena analysed so far. It could thus be tempting to see stem cell clinics as a result of globalisation. However, after initial episodes of interpretative enthusiasm, sociological literature on globalisation has highlighted the near absence of truly global social phenomena in our world. The stem cell clinics, although international in the range of their activity, are no exception to this diagnosis. They could be better conceptualised as global/local phenomena. Without importing any of the normative meanings recently attached to the notion of glocality, I nonetheless believe that, interpreting stem cell therapy clinics as a global/local phenomenon does justice to the reality of them in at least two senses. Notwithstanding

the international character of the therapeutic networks of patients and providers that stem cell clinics exploit, their business is best understood as rooted in very local conditions, namely, the presence of a strong technological infrastructure in one country, and the absence of specific regulations in another. Albeit reliant on worldwide means of communication and marketing like the Internet for promoting their activities and attracting new customers, stem cell clinics offering service across national borders are the result of conditions that have strong geographical connotations. Moreover, the level of transnational engagement is higher where geography plays out as a logistic facilitator, like at the borders between US and Central America, or when the remoteness of places corresponds to regulatory distance between places of extraction and places of injection of stem cell concoctions. These features qualify the phenomenon of cross-border stem cell therapies as a global/local one.

The drug-like framing was intended to exert regulatory power on the emerging field of stem cell clinical research. However, it was exactly this framing that left regulatory room for stem cell clinics to emerge and appropriate a politically and epistemically uncharted territory.

The credibility cycle of the shared model of governance is thus in place. Its aim is to afford stem cell clinical research with the necessary argumentative tools and discursive practices to cope with risk, uncertainty and the presence of alternative framings of the route to stem cell application. As I said, it is now too early to attempt an assessment of how this model is performing in terms of providing social robustness to this scientific enterprise. We are still in an early phase with stem cell innovation, albeit actors are gearing up to compete for delivering the promise of the stem cell technological platform

to patients worldwide. It is likely however, that empirical material will soon accumulate about the actual transactions between interested stakeholders.

The credibility cycle that I described is thus to be taken as a hopefully useful interpretative tool to read into this trajectory of innovation. This tool is thus an explanatory instrument, and is informed by a co-productionist outlook on the reciprocal crafting of a regulatory and epistemic order in biomedical innovation.

So far, in this dissertation, I described but the early movements of the actors involved in constructing and challenging the regulatory regime of stem cell governance. It is possible however that the uncertainties that surround novel biotechnological objects like human cell lines in regenerative medicine, coupled with the shifting power relations between stem cell actors will continue shape the governance model in as yet unpredictable ways. In this sense, also the credibility cycle that I propose as a prism to look into this field of innovation is bound to require adjustments as the field proceeds towards further clinical applications.

I followed framing efforts and contestations where they arose, thus refraining from a strict comparative analysis of national governance regimes. In many respects, such an analysis, at the present stage of stem cell clinical translation, runs the risk of flattening the analytic outlook onto pre-given state boundaries. My analysis has instead shown that roughly the same regime of governability may apply to different countries (as for example happens between the US and the UK with respect to stem cell CCT research). On the contrary, unorthodox framings emerge both in countries where with an established tradition in scientific governance, through loopholes in regulation, and in emerging new bio-economies like China. Moreover, we saw how stem cell actors exploit unbalances

across national boundaries to install their human cell therapeutic practices on a global biomarket that states can hardly control. For these reasons, a more traditional comparative approach looked analytically unsuited to track the early movements into stem cell translational innovation.

Furthermore, individual countries like the UK may seek for hegemonic positions through the certification, standardisation and distribution of banked human cell lines – thus transcending national boundaries in a way that stretches the limits of national authority.

The next step for us is to use deliberative theory to assess the democratic properties of the governance framework that emerged in the course of this dissertation. With this aim in mind, in the next and final chapter I will assess the political features of the shared model of governance and advance a proposal on how to increase the level of accountability in the highly uncertain, but nonetheless highly promising enterprise of translating stem cell science to clinical applications.

Chapter 5: Democracies of translation: towards a deliberative democracy of clinical innovation

In the previous chapters I analysed the formation of a novel governance model for the clinical translation of stem cells. I showed that, contrary to previous models of strict regulatory oversight for embryonic stem cell research, stem cell medicine is developing in the context of a shared model of governance. At present, state agencies and clinical scientists jointly construct stem cell innovation as the development of new drugs to be tested experimentally in the context of controlled clinical trials. At the same time, exploiting blind spots in current regulations and working across state boundaries to their advantage, a number of clinicians are contesting the previous framing and already start commercialising stem cell clinical procedures to an increasing number of patients.

In the present chapter, my aim is to assess the implications of this contested governance regime from a deliberative democracy point of view.

5.1 The quest for deliberative science

A growing body of literature, fed by actual experiences in public engagement initiatives on issues ranging from environmental risk appraisal, to radioactive waste management and urban planning, produced a myriad of deliberative/participatory proposals as to how to democratically reconcile alternative framings of scientifically loaded problems (Fiorino 1989; Laird 1993; Renn *et al.* 1993; Rowe and Frewer 2000; Rowe and Frewer 2004; Santos and Chess 2003; Webler 1999; Webler and Tuler 2001).

Interestingly, the participatory turn (Jasanoff 2005) reaches beyond the limits of academic enclosures. Between the end of the Nineties and the early 2000s, at least three reports suggested the necessity to break up elitist arrangements about expertise and open decision making to wider publics in matters of science and risk management. Namely, the US National Research Council, following an established institutional interests in these matters[21], issued a report in 1997 animated by the realisation that risk management should be conducted by blending scientific analysis and deliberative decision-making (Stern, and Fineberg 1996). Along the same lines, the British House of Lords, drawing on the recognition that public trust in the relationship between science and politics had been undermined by episodes like the BSE crisis, wrote an important report in 2000 where it recommended various forms of public engagement as a way to bring public values and concerns at policy-making sites (House of Lords 2000). Analogously, in 2001, the European Commission issued a white paper on governance aimed at transforming policy-making so as to better connect public decisions and citizens' needs and aspirations, mostly by opening up decisional processes to increased involvement of stakeholders and the public (European Commission 2001)[22].

These documents testify that, both in the US and in Europe, deliberation is understood as a valid development of democratic culture. The reason for applying this normative outlook to stem cell clinical research resides in the nature of the governance

[21] See Health 1983; Communication 1989; National Research Council (U.S.). Committee to Review Risk Management in the DOE's Environmental Remediation Program e Program 1994; Pollutants 1994.

[22] Other examples of the pervasiveness of a deliberative-participatory culture in political bodies may include the Danish Act on Environment and Gene Technology – which allows non-governmental organisations the right to join the evaluation of genetically modified organism (GMO) release applications – and similar provisions adopted by the Canadian and the Australian Governments still in the context of GMO regulations (Einsiedel, Jelsøe, and Breck 2001). Furthermore, in many countries including Denmark, France, UK and the US, ad hoc advisory bodies on issues relative to the development of biomedical and biotechnological innovation steadly include experts in the field of ethics and policy as well as consumer groups, patients advocates and lay citizens too.

model that is emerging in the field of stem cell innovation. In the present context, a number of uncertainties and risks overshadow the development of stem cell science towards clinical application. On the one hand, extremely high expectations characterise this field of innovation, to the extent that, it may well be problematic to ever meet them, or explain to interested publics how slow the developmental process inevitably is. Stem cell science, should early translational efforts fail or result in serious adverse events, runs the risk of being discarded as a promising field thus undermining the very possibility of regenerative medicine. The existing shared model of governance, pulled in contradictory directions by interested stakeholders, may thus well underperform in assuring sufficient degrees of public confidence while creating the most effective conditions for science to steadily proceed into clinical translation.

How is it possible to prevent or at least limit such negative scenarios? How could the development of stem cell innovation be brought on a democratically accountable trajectory? What is needed to cope with the discursive fragmentation of contrasting narratives about biomedical innovation?

The medical promise of regenerative medicine is too important for these questions be overlooked. Moreover, the biotechnology industry, sprout out of steadily increasing public research budgets, represents a driver for economic growth that cannot be ignored. Also in the face of rising costs in providing health to aging populations, the economic opportunities offered by the advent of regenerative medicine cannot be missed. In this delicate situation, careful consideration of the political conditions that may help realising the promise of stem cell innovation is thus needed. The present scenario, as it emerged from my previous analyses, is one of profound disagreement and competing interests in the framing of regenerative medicine. Moreover, the regulatory grip of

involved actors seems insufficient to grant one view to outweigh all the others: regulatory pluralism seems characteristic of the actual governance outlook of stem cell innovation.

Therefore, what is needed is a political appraisal of the capacity of the current regulatory regime to bring about accountable governance to the field, while leaving the door open to the possibility of adapting to present uncertainties and future new findings on the safety and efficacy of stem cell based-therapies.

As I tried to show elsewhere in this thesis, it is through deliberative democracy that, in my opinion, accountability and legitimation can be infused into the governance structure of contentious biotechnological innovation. In particular, it is important to recall that deliberative democracy, as I introduced it in chapter one, aims at crafting the process of public decision making as one of "collective deliberation conducted rationally and fairly among free and equal individuals" (Benhabib 1996, 69).

It is thus preliminarily useful to assess the democratic potential of what we, thus far, described as the shared model of governance of stem cell translational activities.

To this aim, in the next section, I will draw on existing assessment criteria to perform an evaluation of the democratic quality of innovation in the field of stem cells.

5.1.1 Democratic assessment

According to the deliberative theory of democracy, the public legitimation of political decisions rests on the quality of the public discourse that precedes it. In the public sphere, discourses informally circulate that produce evidence, arguments and persuasion as to the better or more just solutions to important policy problems. In current democracies, these very general principles have been implemented into the practical life of nation states, especially at the local or regional level. This phenomenon is resulting in a

profound transformation of the very aspect of democratic polities as they try to innovate the political rituals of representative institutions so as to yield more accountable, more inclusive, and less divisive public decisions to the problems of political communities. In an effort to foster a deliberative turn in democratic life, various mechanisms of inclusion attempt to enlarge policy forums to the participation of concerned stakeholders and lay citizens.

In concomitance with these political novelties, an articulated body of literature developed evaluation criteria for assessing the deliberative quality of political initiatives. However, in the face of a marked diversity of approaches, it is not possible to say that there exists something like a universally agreed-upon list of criteria whereby assessing the effectiveness and consistency of governance activities from a participatory-deliberative perspective. It is nonetheless possible to isolate a kernel of benchmarks that are generally used in these evaluative exercises in the literature. Jason Chilvers has recently produced a version of such a benchmark set of criteria in an interesting study that included both scholarly accounts and practitioners' viewpoints on deliberative appraisal activities (Chilvers 2008). What Chilvers proposes is therefore a set of criteria that lends itself to some degree of overlapping consensus.

In what follows – freely drawing on Chilver's grid (*ivi*, 176, Table 3) – I will thus assess how the shared model of governance in stem cell innovation fares with respect to a deliberative-participatory account of democratic decision-making, legitimation and accountability.

My own version of the benchmark comprises the following baseline criteria to assess the deliberative quality of biomedical regulatory regimes: fairness of inclusion with respect to the engagement of all potential stakeholders; correct timing of engagement

with respect to the technical development of innovation; constructive role of expert knowledge in the elaboration of technological appraisal; implementation of characteristic deliberative virtues into the political discourse – that is, interactive engagement, symmetry between participants, openness to alternative framings, social learning and independence of facilitators.

Those criteria express, in a very broad sense, the ideal characteristics of deliberation as a legitimising procedure. In applying them to the appraisal of a given techno-scientific phenomenon, one should however consider two things. First, whatever the level of institutionalisation[23] of and commitment to deliberative politics, no actual governance regime will ever fully meet the ideal. Second, and more importantly, the use of the above criteria need not be restricted to the appraisal of explicitly deliberative exercises. The intuitive idea behind deliberative theories of democracy is not that representative democracy is totally at odds with the ideals of deliberation – and thus morally wrong or politically illegitimate. Rather, deliberative democrats conceive of direct participation in deliberative exchange as being the tentative realisation of an ideal public sphere where all are included and no one's point of view is excluded on the basis of the social position of the speaker[24]. Members of the public sphere, in other words, recognise each other as free and equal, thus granting each member with the same rights to decide politically. However, it has to be stressed, this idea is not the backbone of deliberative democracy only, as it informs all other different frameworks of democratic thinking as well. In the words of two distinguished political theorists,

[23] "Institutionalization is the process by which a body acquires a definite way of performing its functions – a way that sets ita part from its environment and that is independent of the membership and issues of the moment" (Hibbing 1988)

[24] This intuitive ideal has been fully formalised by Jürgen Habermas in his famous writings on the "ideal speech situation" (Habermas 1970; Habermas 1987).

> «democratic arrangements have the intrinsic virtue of treating those who are subject to binding collective decisions with respect, as free and equal: 'the person of the humblest citizen is as sacred and inviolable as that of the first magistrate.' [25] Thus, the judgements of citizens, who are expected to govern their conduct in accordance with collective decisions, are treated by the processes of collective decision as equally authoritative. Though decisions will rarely, if ever, be unanimous, no one's judgement of the proper rules of cooperation is treated as having greater weight. Given the back-ground conception of citizens as free and equal, any assignment of differential weights to the views of different citizens is a form of disrespect (unless it can be provided with a suitable justification)» (Cohen and Sabel 1997, 319).

These last considerations, leads us to consider that deliberative criteria can indeed be used to assess non-deliberative political processes as well as deliberative ones, and to produce possibly useful political indications to ameliorate the democratic quality of the process under scrutiny.

The fairness of inclusion

A first intuitive specification of the idea of democratic participation prescribes that all interested and affected parties be included in the deliberative process that precedes a publicly binding decision. As a consequence, inclusive participation should follow criteria of representativeness in the selection of the stakeholders whose viewpoints need to be taken into (discursive) consideration.

[25] (Rousseau 1970, 3.14)

With respect to this aspect, scientific controversies frequently show the democratic inefficiency of traditional governance strategies. As we saw in chapter 3.I, contemporary science stemmed out of a blind delegation model that left scientists alone to decide about the content and timing of their professional activities. Furthermore, as one can appreciate from nowadays classical STS works on scientific advice to public decision-making (see, for instance, Jasanoff 1994), this delegation model reverberated in the exclusive privilege afforded to scientists to directly interact with decision-makers in the case of controversies about contaminants, carcinogens, radioactive waste and chemicals used in the food industry, to name but a few classic examples. In the case of r-DNA, we saw that a self-regulation model further exacerbated the exclusive character of scientific governance. With the advent of embryonic stem cell research (as well as in the GM crop/GM food controversy), however, such political configuration simply proved unable to contain and manage the amount of moral disagreement that such strand of innovation gave rise to.

With respect to the emergent governance configuration of stem cell clinical translation, as one can appreciate from our previous analyses, the situation is mixed. Certainly, not all interests and viewpoints are granted equal weight in all the political sites (both institutional and informal) where discourses circulate and decisions are taken as to the future of stem cell innovation. Alternative framings of stem cell innovation sit at opposite sides of a scientific and regulatory divide, and only enter in contact at adversarial occasions. Furthermore, the voice of patients is substantially less powerful than that of scientists, practitioners and regulators[26]. Other important stakeholders are

[26] I would just like to mention that this last feature needs not necessarily be the case, as it is sometimes argued in consideration of the vulnerable conditions of diseased individuals. For instance, the engagement of patients' groups has certainly played a major political role in the case HIV-AIDS research in the States (Epstein 1998), and Muscular Distrophy in France (Callon and Rabeharisoa 2008). For a general appraisal of this theme, see (Epstein 2007).

private funders of clinical translation and patent holders. Their presence is not immediately visible in the public debate taking place on specialised journals and on the media. It is however evident that their influence is decisive to the development of stem cell innovation. This situation introduced in the debate arguments based on the doubt that commercial interests insidiously articulate the vision and political strategies of stem cell researchers. A major preoccupation with the hidden relationship between scientists and their commercial partners concerns unscrupulous behaviours with respect to research subjects and patients. Nevertheless, we have also recognised that a culture of concern for the ethical consequences and social implications of stem cell clinical research is undeniably in place in the declared intentions of international scientific societies. We saw that ethicists and social scientists are co-opted in the advisory bodies that regulate clinical translation, and also called to contribute to research guidelines.

It is however evident that no truly deliberative forum exists where all stakeholders can meet on a par, discuss and shape the course of stem cell innovation according to a shared vision of how the latter should look like. The regulatory panorama is instead fragmented and dominated by adversarial and exclusivist attitudes. This, however, is not imputable to a lack of democratic civility, or at least not only to that. Rather, stem cell innovation is still technically uncertain, meaning that, as I said from the beginning, the actual route of stem cell-based regenerative is truly hard to anticipate. In this situation, stakeholders run the risk of being framed-out by alternative visions of stem cell medicine, and thus compete for safer positions in the regulatory landscape. At the same time, interested stakeholders compete also for another important resource, namely public support. They thus enact their own strategies to build credibility (see *supra*, 4.3.2 on the credibility cycle), irrespective of the consequence that those activities have on the discursive position of other stakeholders.

In my opinion, in the current context, the field of stem cell medicine thus sits at a perilous junction. On the one hand, actors need to show that their interests are legitimate and their framings convincing, if they want to look as socially accountable and reliable innovators. On the other hand, however, their way of pursuing this objective relies on framing strategies that may be exclusive, and thus at odds with the inclusiveness that democracy requires as a public hallmark of legitimacy. All the more so, such intricate dynamic runs the risk of eroding both the authority of the involved parties (scientists, clinicians and regulators) and the civic capital of democratic culture that preserves our polities upon divisive controversies. In other words, the present configuration of the governance of stem cell translation looks ill equipped to prevent both a credibility crisis and democratic erosion.

To address both concerns, it seems to me that the implementation of participatory initiatives could represent an opportunity for innovation to take place in a much more accountable way. Fostering inclusion in technological development responds to the realisation that science and technology are «increasingly recognized to be open to individual creativity, collective ingenuity, economic priorities, cultural values, institutional interest, stakeholder negotiation, and the exercise of power» (Stirling 2008, 263). Therefore, to begin with, widening the panel of relevant experts to include humanists (i.e. bioethicists and social scientists) may enhance the credibility of stem cell governance and the open character of the public discourse about it. Moreover, should patients also be involved in a deliberative exercise about stem cell innovation, they could contribute to the creation of a socially more favourable climate around early translational efforts in this field. In particular, patients could play a more active role in setting the priority agenda of stem cell innovation and in trimming the ethical criteria that regulate the involvement of research subjects in clinical research (see *infra*).

The timing of inclusion

As noted by a number of scholars in the field of STS and Technology Assessment (see *infra*, 5.2.1), innovation can avail itself of various forms of political inclusion. However, the time point when stakeholder inclusion takes place is not a secondary issue. In the ambit of an emerging institutional awareness about the desirability of more inclusive policy processes, and in the wake of science-related crises like the BSE case in the UK and the GM food controversy in Europe, scholars have started to appreciate how the timing of inclusion might indeed play a primary role in science-related public controversies.

The field of policy oriented STS has indeed generated a number of studies on the opportunity for inclusion to take place as early as possible in the very framing phase of technological trajectories (Grove-White, Macnaghten, and Wynne 2000; Marris *et al.* 2001; Wynne 2001; Wildson and Willis 2004). Although this cannot be considered a golden rule that suits equally well in all circumstances, it is conceivable that, in this initial phase of stem cell translation, more opportunities are granted to interested parties to shape the future of stem cell innovation. This must happen before interests crystallise to the point of causing what has been called sociotechnical lock-in (Callon and Rabeharisoa 2008, 246). What is meant with that expression is that the development of innovation may take a route determined by the privileges, both political and economic, acquired by one or few technical and scientific options. In these circumstances, stakeholders have fewer opportunities to influence the trajectory of innovation than in the early phases of technological framing.

It may be argued, however, that it is in a sense already quite late for upstream inclusion to take place in the case of stem cell medicine. Certainly, dominant framings have already occupied the political space, but, once again, the future of stem cell clinical development is uncertain enough to afford occasions of effective inclusion to occur nonetheless. All this notwithstanding, in terms of early inclusion of a broad set of interests and viewpoints, the present regulatory regime of stem cell innovation seems wanting, notwithstanding some timid efforts at co-opting patients' representatives and humanists at decisional venues (see the case of CIRM-mandated SCROs). Therefore, even if stem cell innovation has not so far included large panels of stakeholders in the definition of shared priorities and socially affordable framings, there is still some room for intervening upstream on the technical development of the field, especially at the level of specific translational initiatives (see *infra* 5.2.3).

Expert knowledge in participatory appraisal

What is the role of expert knowledge in the regulatory decisions on stem cell translation? In my previous analyses, I highlighted a relatively insulated circulation of scientific information among scientific experts and regulators. The production and certification of scientific knowledge that is necessary for the technical and regulatory advancement of the field (namely pre-clinical and clinical scientific data about safety and efficacy) takes place in the innermost communications between regulators and IND applicants – in the case of standard CCTs – and between practitioners, ICMS and, to some extent, patients – in the case of stem cell clinics. Therefore, scientific information is not used to inform participated deliberative decisions in a truly meaningful sense. According to Chilvers' criteria, scientific knowledge in effective participatory governance should be produced either to support deliberation or to respond iteratively to the needs of deliberators and, finally, should be transparent to participants, thus "making underlying

uncertainties and assumptions explicit" (Chilvers 2008, 246). In the present regulatory framework however, no such inclusive process is actually taking place. As a consequence, scientific knowledge is actually being produced and made public to allow the clinical control of cellular entities, on the one side, and to strategically secure positions of authority and control over stem cell-related activities, on the other.

Deliberative ways

According to deliberative theories, a participatory exercise should build on a diverse set of discursive virtues to fulfil its legitimating role. In the case of technology-related issues, deliberative participation should be: interactive, symmetrical, able to emphasise rather than reducing diversity, and conducive to mutual social learning (adapted from Chilvers 2008). To what extent does the current shared model of governance, albeit not originally conceived in deliberative terms, allow those virtues to shape the trajectory of stem cell innovation? A certain degree of interactivity between interested parties is present at the already mentioned level of formal and informal communication between scientists and dedicated advisory committees in regulatory bodies. To a certain extent, these exchanges enjoy some degree of symmetry, but only so far as they involve scientists on both sides. Nonetheless, they tend to exclude any other interlocutor both in terms of linguistic specialisation and in terms of actual possibilities of interaction.

In another sense, scientists and clinicians are truly trying to produce public awareness about the possibilities of stem cell medicine. It has however to be noticed that such efforts often portray the therapeutic promise of stem cell science as imminent and revolutionary. If it is true that scientific knowledge on the biology of stem cell accumulates quickly, it is also worth noticing that the route to the clinical application of that knowledge is still conceivably long and uncertain, both from the scientific and from

the regulatory point of view. Therefore, those efforts at rising public attention on the clinical benefits of stem cells may indeed result in hyping the promise and downplaying the difficulties of stem cell translation. What is worrisome about this tendency is its effect on the democratic governance of stem cell innovation. Public hype about stem cells certainly played a positive role in securing public research funding in certain circumstance (see the 2004 Proposition 71 referendum in California for example). But in the long run, it has produced a climate of impatience towards the delivery of stem cell applications that, on the one hand, put pressure on innovators and investors while, on the other, created the conditions for cunning practitioners to offer stem cell treatments to credulous patients. In other words, an unfaithful picture of the state of stem cell innovation is conducive to an unbalanced public discourse on this complex issue, thus resulting in an unfavourable climate and problematic social phenomena.

As to patients, they can indeed interact, for instance, with both ISSCR and ICMS in seeking information about stem cell trials and clinics. To this point, the end of the ISSCR 'submit a clinic' initiative severed an emerging link between patients and academics that might have been developed in fruitful directions[27]. As a matter of fact, however, those latter forms of communication are scarcely symmetrical, in the sense that one of the speakers retains full epistemic authority over the other. To my knowledge, the attitudes, expectations and values of the patients that contact scientific societies are not systematically and publicly reviewed, nor are their reactions to the information they receive are monitored by independent observers. These latter activities, would be convenient in view of gaining insight into the patients' own framing of stem cell innovation. Such insight, I would like to suggest, would indeed be precious if eventually used to inform deliberative exchange.

[27] I am grateful to Giuseppe Testa for pointing out this idea.

Along the same lines, interaction and symmetric consideration of discursive contributions are likely to open up the regulatory process to the widest possible variety of interests and viewpoints. This possibility has recently been proposed as a hallmark of effective inclusive-participatory processes (Stirling 2008). In the vein of not considering stem cell innovation as a pre-determined, inevitable and locked-in process, the construction of regulatory order around stem cells should be favourable to the emergence of «any inherent indeterminatcies, contingencies, or capacities for agency» (*ivi*, 279). Openness to diversity, both in the viewpoints about innovation and in the language through the latter are expressed, is indeed conducive to the realisation of four important features of legitimate democratic governance. First, diversity is more likely than authoritative closure to result in increased levels of representativeness. Second, deliberative decisions are more likely to be rational through an open process of cross-checking of the available policy options, rather than through exclusive appropriation of decisional power by individual stakeholders. Third, through opening up the public debate to a variety of viewpoints, it is to some extent possible to anticipate or to prevent conflicts arising form exclusions that are perceived as unjust and undermining of democratic equality. Fourth and last advantage of openness, should a variety of interests, value and ideas be taken into account in a deliberative process, resulting decisions would be democratically more justified. The reason for this surplus of legitimation is that, in ideal conditions, openness favours *argumentative opting-out* over *strategic framing-out* of given policy options and innovation trajectories. In an ideal deliberative process, all options are taken into consideration possibly without biases in favour or against any of them. It is however through argumentative exchanges that, at the end of the process, some options are discarded (argumentative opting-out) and some others are retained and eventually implemented. Furthermore it is also possible that, through deliberation, new

political or technological options emerge, or initial ones are modified via non-dominated discursive exchange. This feature is thus intended to preserve policy-making from enacting democratic erosion (see *supra*, chapter 1.7).

The public discourse about stem cell innovation is partially open to alternative framings, values and imaginaries about the future of stem cell medicine. Nevertheless, lack of interactivity and symmetry fosters an adversarial relationship among bearers of different visions and contrasting interests. Furthermore, openness is incomplete with respect to patients' voices and commercial actors, whose discourses lack publicity and tend to remain hidden in the backstage.

Creating more structured occasions of deliberative engagement between stakeholders should also be conducive to enhance social learning. This means that different actors may end up learning from each-other directly through sustained public engagement. Together with interaction, symmetry and openness, social learning draws on the democratic commitment of acknowledging all affected parties as free, equal and equally entitled to have their voice heard in public deliberation. This is beneficial to the elusive cultural task of protecting associate life from democratic erosion, but it also advantages stakeholders in giving them the opportunity of knowing more (and better) about the inhabitants of the political landscape in which they act.

Overall, however, the governance of stem cell translation fares quite poorly with respect to these ideals of deliberative democracy. Regulators, public funding agencies, scientists, patients and the industry have not so far been engaged in meaningful deliberative initiatives and thus, as one can easily imagine, they had but few and limited chances of practicing the virtues of deliberative citizenship. Lay citizens, as well, have

mainly been called to intervene in the occasion of referenda about stem cell public funding – indeed a deliberatively poor political activity.

5.2 The democratic control of clinical innovation

My analyses in the previous section demonstrate that the emerging governance regime of stem cell innovation is sub-optimal in deliberative respects. The main problem that I see with the democratic character of stem cell governance (or the lack thereof) is the preference afforded to a politically dangerous way of coping with uncertainty and diversity of technological visions. At present, politically interested and active parties tend to adopt muscular regulatory attitudes to expel those that they perceive as adversaries from the territory of practicable innovation. Others, thus reacting through an analogous strategy, contest the regulatory authority of public agencies and of some sectors of the scientific establishment by discrediting their intentions on moral grounds and by constructing their own *ad hoc* epistemological commitments. In my analysis, I tried to remain neutral with respect to the oppositions – political and scientific – that I described. This neutrality followed through in my deliberative assessment of stem cell innovation governance. This resulted in the advancement of very general political indications in the last section that, as the reader will have noticed, were more procedural that substantive in character. My main aim here, is to stress once again that 'framing-out' the activity of stakeholders that are perceived as adversaries is not conducive to a stabilised/normalised governance of innovation. In our case this is true even of framings that I, personally, do not find attractive from both a scientific and an ethical point of view. According to the normative outlook that I decided to adopt as a methodological tool for my analyses, policy dispensations that are the result of framing-out activities, are conducive to much less accountable outcomes than other, deliberation-friendly strategies. According to the

ideal of free and unconstrained circulation of discourses, a regulatory regime would be much more legitimate if it resulted from fair deliberation. As far as possible, *strategic framing-out* should thus be replaced by *argumentative opting-out* of innovation options. This means that, if a given trajectory of innovation is discarded, an argument-based public rationale is provided that does not rely on the relative power positions of the speakers. In ideal deliberative conditions, actors do not compete for power but for persuasion through justifying discourses. In tune with the ideals of deliberative engagement, "the reciprocal requirement to put forward reasons and to respond to challenges will tend to eliminate irrational preferences based on false empirical beliefs, morally repugnant preferences […] and narrowly self-regarding preferences" (Smith and Wales, 2000)[28]. Obviously, abiding by this very abstract ideal is problematic. But I have specified criteria and virtues that, allegedly, correspond to the ideal and may thus facilitate its – always tentative, partial and provisional – realisation into real political life.

Deliberatively oriented initiatives could contribute to a more democratically accountable governance of stem cell innovation especially in the face of present uncertainties about its realisation. In this sense, it is advisable that interested stakeholders, upon their own initiative or under the aegis of dedicated political *stimuli* engage in more frankly deliberative activities to foster the creation of less adversarial conditions for techno-scientific innovation.

Obviously, as highlighted in the case of scientific technology appraisal (Jasanoff 1990), also participatory deliberation is sensitive to framing (Stirling, 2008, 275). This does not undermine, however, the value of spending political efforts on trying to mitigate the erosive consequences of framing-out strategies in controversies about

[28] See also Miller 1992 on the "moralising effects of public discussion.

biotechnological and biomedical innovation. Even more so, in the case of promising fields of biomedical research the systemic political effects of the governance of innovation bear consequences on the well-being of patients and research subjects, thus calling for an even more pressing commitment towards responsible and accountable policy-making.

In the case of stem cell innovation, this translates in resorting to deliberation to tackle the emerging sticking points of the field, that is, primarily, the concern that commercial interest, albeit legitimate, may outweigh considerations of safety and respect for patients and research subjects' autonomy. To this aim, technology assessment (TA) has developed ways to cope with discrepant stakeholders' framings in deliberatively accountable terms – as the coming sub-section illustrates. I what follows I will thus show how participatory and constructive TA could serve the aims of fostering democratic accountability in the governance of stem cell innovation.

5.2.1 The technological assessment of biomedical innovation

Technology assessment (TA) is the activity, typically conducted within parliamentary bodies, whereby technological options are evaluated and their consequences are discussed with the aim of bringing their evolution and development under various forms of political control.

TA emerged in the late Sixties, mainly as a consequence of ever more pressing environmental concerns and under the growing demand for increased public justification for science-related policy choices. The beginning of TA as an institutionalised activity is generally placed in 1972, when the Office of Technology Assessment was established within the US Congress[29]. About ten years later, a number of European parliaments

[29] I cannot go into the details of the OTA activities in this dissertation. See (Bimber and Guston 1995; Bimber 1996) for reference.

adopted analogous dedicated departments to cope with activities of TA[30]. TA is thus to be intended as a mandated activity that, generally, is prompted by a political actor and implemented either by this actor itself (as it was the case in early parliamentary TA) or by co-opted specialists and stakeholders.

The overall inspiration of TA comes from the perceived necessity to "reduce the human costs of trial and error learning in society's handling of new technologies, and to do so by anticipating potential impacts and feeding these insights back into decision making, and into actors' strategies" (Schot and Rip , 251).

The aims of TA are multifarious. They comprise a number of objectives that should constitute the core of decision making processes about science and technology, and they originally include: strengthening the influence of public decision-makers by firstly providing them with the necessary information about scientific innovation and technological phenomena; exploring available technological alternatives and assessing them; providing more legitimate and politically more accountable policy decisions; alerting decision-makers and the public about undesirable consequences of technology as early as possible; supporting and stimulating the emergence of social groups' visions about technological development; sustaining the development of socially desirable and useful technologies; promoting public acceptance of science and technology; uplifting a self-reflexive attitude in scientists and innovators about their social responsibilities (adapted from van EiJndhoven, 1997, 270). Overall, the final product of TA initiatives is a series of policy recommendations that legislators, who mandate the initiatives in the first

[30] The list of countries that initially engaged in TA at the parliamentary level comprises: Denmark, France, Germany, The Netherlands, United Kingdom and the European Parliament (Vig and Paschen 2000). Other countries in the European area have more recently adopted TA departments, and joined the latter to form European Parliamentary Technology Assessment (EPTA) network, namely: Catalonia, Finland, Flanders, Greece, Italy, Norway, Sweden and Switzerland. This testifies of the widespread realisation that technology has important social and political consequences that, as far as possible, had to be coped with in politically accountable way. For details about parliamentary TA in Europe see (Vig and Paschen 2000).

place, are variously committed to take into account. It is not necessary however, that TA initiatives result in new legislation.

As one can grasp form this brief description, the theoretical background of TA, as well as its various realisations, stress the joint evolution of technology and society thus going hand in hand with the co-production approach to the study of scientific and technological phenomena, and with a deliberative-participatory appraisal of democratic policy on science and technology (Schot and Rip 1996; Guston and Sarewitz 2002).

Moreover, TA is often described has having to do with tackling what has been called the Collingridge dilemma (Collingridge 1980). In his 1980 book on the social control of technology, social scientist David Collingridge famously depicted the governance of technological innovation as being impaired by the unpredictable trajectories that the development of a new technology is open to take, both at the technical and, *a fortiori*, at the societal level; on the other hand, Collingridge also observed that, once fully developed and socially entrenched, technologies are unlikely to lend themselves to political steering initiatives and control – thus putting politics in front of a governance dilemma. Therefore, regulating innovation early on is made difficult by the uncertainties and the unknowns that surround technological development; however, intervening to create a governance regime around a given technology once it has emerged is impaired by the fact that technologies, once available, rapidly shape widespread social practices.

It is clear that the Collingridge dilemma affects the development of stem cell medicine in a very direct way. On the one hand, it is presently hard to anticipate where and how the technological platform of stem cells is going to deliver its applicative fruits and how the latter are going to bear on the life of future patients. On the other, we saw that the risk of socio-technical lock-ins appears to be a likely result of involved actors'

framing strategies. For this reason, stem cell innovation seems to fit well the application of TA, as a way to work out the difficulties the dilemma tries to capture.

5.2.2 Participation through technology assessment

TA has developed in many diverse strands, and has proposed and implemented a number of strategies to cope with the dilemma[31].

Of relevance to the analyses that I developed in the previous sections, *participatory* TA (Joss and Bellucci 2002) certainly has some suggestions to offer as to how a climate of public consensus and social responsiveness could support the development of stem cell medicine. The core tenet of the participatory strand of TA is the idea that technology assessment initiatives should be conceived as a way to "empower democracy in influencing the directions taken in technological development" (van Eijndoven, 1997, 258). The focus is thus on effective methods to foster public engagement of lay citizens in the discussion of technological options with the aim of creating socially robust conditions around scientific and technical novelties. Moreover, participatory TA may well inform legislation, but it need not be conceived as undermining the constitutional privileges of elected representatives.

Various methods have been used to involve the pubic in deliberative exercises about technology in the recent past. They range from focus groups, consensus conferences, citizens' panels (Burgess, O'Doherty 2008, Fishkin, Luskin & Jowell 2000, Fowler and Allison 2008), public consultations (Fiorino 1990), scenario workshops (Ogilvy 200), citizens' juries (Smith and Wales 2000), citizen's review panels (Wakeford 2002), open-space methods (Owen 1997), elicitation techniques and public surveys (McKewon

[31] It is generally assumed that TA comprises a number of variants that, according to the focus of their interests can be classified as follows: expert TA, participatory TA (also known as public TA or Danish model), parliamentary TA, constructive TA (or Netherlands model), health TA.

and Thomas 1988; Fransella et al 2004). Being TA eminently initiated *via* political initiative, choosing among this array of participatory techniques without a clear picture of the specific political, social and scientific context in which such participatory TA should be pursued would be a scholastic exercise. However, I would suggest that political actors, such as regulatory bodies (e.g. EMA or FDA) and parliaments could act as facilitators of inclusive-participatory initiatives aimed at highlighting stakes and hurdles of stem cell innovation and, eventually, provide recommendations for their political handling.

One possibility, among many other feasible ones, is to involve citizens in what have been called 'citizens' juries' (Smith and Wales 2000) or 'planning cells' (*Planungzellen*) as they are labelled in Germany. A citizen jury, similar to juries in legal contexts, is a group of citizens selected randomly or according to representational criteria that vary from case to case. Those who accept to sit in the jury are engaged in a deliberative exercise. Typically, citizens' juries amount to twelve to twenty-five people who convene in a dedicated location for two to four days. Participants are provided with information materials to let them become familiar with the issue under discussion and are exposed to expert witnesses and stakeholders' reports. Following this initially passive phase, the jury starts discussing under the guidance of a moderator. In this phase, jurors are allowed to interrogate experts and stakeholders, including – if they deem it appropriate – those that were not initially involved in the initiative. In the next step, jurors deliberate about the issue and produce a report that contains recommendations to the sponsoring institution as to how to act with respect to the matter at stake. The promoting institution, is then supposed to reply to this document and/or to implement those recommendations into policies or guidance documents. The whole process is public (it can include observers from the media) and is steered by the moderator in an unbiased way. To ensure this latter characteristic, rules of discussion can also be established

beforehand in a preliminary meeting between organizers, promoters and selected jurors (see for example Boniolo and Di Fiore, 2010).

According to the accumulated experience on the use of citizens' juries[32], this instrument proved useful in a number of respects. A major advantage of participatory TA initiatives is to stimulate the formation of political opinions that may not be present in the citizenry beforehand. The public character of participatory TA is generally assumed to be a vehicle fostering the formation of opinion, and eventually of political will, of lay citizens about technological innovation. Thus, in the case of stem cell innovation, the public may not have already fully formed ideas about the stakes of this technology and its impact of society and individuals. In this respect, TA can encourage a public debate on matters that, otherwise, may remain hidden to the public eye. The emergence of public debate is thus to be seen as a moment of political legitimation whereby the interests and the reasons of innovators are brought to interact with wider societal concerns and needs. Especially in the case of technologies that, like stem cells, present various levels of ethical and societal implication, the expected result of this engagement between innovators and society at large is the creation of a politically more stable climate around innovation, one that is conducive to a more efficient management of possible controversies and disagreements.

Participatory TA initiatives should be oriented to build widespread public awareness about the problems and opportunities of stem cell innovation, and should thus primarily be directed to involve lay citizens. It can thus be up to the latter to actively include all interested and affected parties in their assessment activities, from scientists to

[32] The Jefferson Institute in the US, the Research Institute of Citizen Participation in Germany, and the Institute of Public Policy Research, the King's Fund Policy Institute and the Local Government Management Board in the UK have run several participatory-deliberative initiatives with citizens' juries. For reference see Stuart, Coote and Kendall 1994 and Coote and Lenaghan 1997.

clinical researcher, from practitioners to patients. To this latter group, it is not said that patients are already organised as a structured group, with clear interests, objectives and identities. I thus reckon it is of fundamental importance that the participatory exercise helps patients organise and speak out their visions about technological changes that may affect them. Therefore, it is crucial to foster their direct inclusion and closer collaboration both as research subjects and possible future users of stem cell medicine. To this end it is critical that, through the participatory exercise itself, their interests, viewpoints and identity acquire a more structured and publicly visible articulation. In other words, a primary outcome of participatory TA initiatives should be of letting patients emerge as key players of stem cell innovation. Where this happened in the past, patients' groups proved able to help biomedical development financially, by campaigning for fund raising, scientifically and in terms of social credibility (Callon and Law 1982; Epstein 1998; Epstein 2007; Callon and Rabeharisoa 2008; Epstein and Peters 2009). Moreover, different patients' groups may develop different ethical stakes, both in participation to research and as final users of future medical technologies, that current ethical standards and self-contained guidance documents can hardly be aware of. Patients can thus represent a precious ally of scientific and medical development of stem cells both as self-aware research subjects and interested users.

The fact that identities, political positions and wills to a great extent are likely to form within the participatory TA exercise, instead of being fully available before it, is consistent with the idea that deliberation is a process whereby reasons are exchanged and initial opinions are bound to be modified through this exchange. It is thus enacting a distinctive feature of deliberative democracy that participatory TA is expected to bring legitimation to the democratic handling of technological development.

5.2.3 Constructive technology assessment

The importance of technology users as active determinants of innovation has been stressed by another strand of TA, one that goes under the heading of constructive technology assessment (CTA) (Rip, Schot, and Misa 1995; Smits, Leyten, and Hertog 1995). The latter, also seems well equipped to steer the emergence of stem cell medicine towards a socially accountable and more robust development[33].

The main tenet of CTA is the idea that the role of stakeholders should not be limited to the anticipatory appraisal of a given technological development (like in canonical TA). Rather, according to CTA, the societal aspects of scientific and technological novelties should be, and can in various ways be translated into actual design criteria for the technology under consideration.

CTA is thus conceived to let interested stakeholders directly participate in the framing of a technological innovation, in response to both the visions of innovators and the necessities of societies. As stem cells are beginning their journey towards clinical application, more doubts than certainties insist on the exact development of their technological trajectory. This feature is also reflected in the complex and, as yet, uncertain governance of this early phase of clinical translation. Therefore, the possibility of influencing the very technical development of technology seems particularly important in the case of technological platforms that, like stem cells, as yet do not provide clear indications as to which application they will provide and with which direct consequences, both positive and negative, on people's lives.

[33] CTA grew out of the specific approach to technology assessment taken by this activity in The Netherlands in the early Eighties. I do not have space here to reconstruct this historical development, nor to let the reader appreciate its peculiarities with respect to other strands of TA. For more detailed reference about these topics, see (van Eijndoven 1996; Schot and Rip 1997)

CTA needs not take place at the level of representative institutions or executive powers. Even though institutionalisation is not contrary to the aims of CTA, this approach to technological appraisal emphasises the fact that members of the civil society, variously organised, can bring legitimation to policy decisions from outside traditional political institutions. This is in line with the propensity of deliberation to take place in the so-called middle democracy (Gutmann and Thompson 1996). To this point it is worth recalling that IFOM-IEO (the research institution I work at) recently elaborated specific guidelines to foster deliberative engagement with external stakeholders (Boniolo and Di Fiore, 2010)[34]. What is interesting about this initiative is that deliberation on the social and ethical consequences of biomedical research occurs directly at the site where that research is generated experimentally and translated clinically into hopefully successful new treatments. I contend that this kind of activities is praiseworthy, and likely to stimulate public awareness about the aims and methods of biomedical innovation. The proactive involvement of scientific institutions at the level of deliberative exchange with relevant stakeholders and the public, I believe, is bound to augment the legitimacy and public accountability of innovation irrespective of the fact that it takes place outside traditional political locations.

I am thus suggesting that the governance of stem cell innovation could be brought under more accountable political control through similar activities and, in particular, by means of a CTA-based approach to technological assessment.

Within the toolbox of CTA, one methodology seems particularly apt at realising the purpose of direct stakeholder involvement in the discussion and planning of

[34] In November 2011, IFOM-IEO has also launched the "YouScientist" platform, that is, a programme aimed at engaging lay citizens within the research institute to spread public awareness about the making of scientific knowledge and its translation to the clinic.

technological options: strategic niche management (Kemp, Schot, and Hoogma 1998) can be the basis for constructing a more accountable governance of stem cell medicine in the coming years.

Strategic niche management (SNM) is defined as "the creation, development and controlled phase-out of protected spaces for the development and use of promising technologies by means of experimentation" (Kemp, Schot, and Hoogma 1998, 186). This activity points at a number of expected outcomes. In particular, it aims at assessing the social desirability of the available technological options, primarily through learning about stakeholders' expectations and interests directly from the TA process. Furthermore, it fosters to stimulate social changes that are necessary for the correct diffusion of a technology according to the preferences of relevant stakeholders (*ibidem*). Therefore, in general terms, the aim of strategic niche management has been defined as "the construction of a constituency behind a product – of firms, researchers and public authorities. (*ibidem*).

SNM is thus to be conceived as an interactive process whereby different stakeholders join forces in the context of a pilot experiment with a new technology and contribute to the definition of technological options. This activity is therefore aimed at integrating stakeholders' visions in the very fabric of the technology itself. A field of innovation like stem cell medicine, that I presented as particularly unstable in terms of design, would thus benefit from interactive, public and inclusive experiments in SNM. Furthermore, being biomedical innovation traditionally attained through clinical trials, the field easily lends itself to pilot experiments where inclusion and participation play a new constructive role in the development of stem cell products. By the same token, however, given the present contested framing of stem cell innovation through state-controlled clinical research, this kind of CTA may also encounter some resistance. However, should

clinical trials with stem cells (or at least a few of them) be performed under the guiding principles of inclusive and publicly visible CTA, the burden would be on the shoulders of critics to display similar levels of commitment towards public accountability and respect for the expectations of concerned publics, and patients in particular. By enlarging the scope of participating stakeholders beyond public regulators and industry-backed scientists to patients' groups and non-governmental organisations, SNM could thus raise the democratic quality of innovation development to a higher standard of accountability, thus feeding public credibility and social robustness into the early phase of stem cell medicine.

Moreover, it is also expected that SNM, and CTA in general, be conducive to a better appraisal of the cultural, psychological and social dimensions of technological change – which, in the case of biomedical innovation, is of substantive political advantage (*ivi*, 190). A further benefit of SNM is the fact that, during the pilot experiments, enabling conditions, both organisational and economic, are discussed among stakeholders at an early phase of technological development. This is of the utmost importance for a biomedical technology that is not only expected to become entrenched into already existing and already complex health-care systems, but also promises to potentially change health-care provision in quite substantial ways.

According to CTA, such experiments should thus promote the building of new networks that are able to shape the direction of technological change in socially accountable ways.

In the last two sections I suggested that stakeholders, expert communities, citizens and public regulators can be brought together *via* their common involvement in

technology assessment activities. The outcome of such initiatives needs not be new legislation, although this may turn out to be the case. Nevertheless, the organisation of publicly visible workshops and deliberative venues, or the production of public reports and white papers are in themselves interesting ways of stimulating public awareness and complementing the traditional mechanisms of democratic decision-making in complex areas such as scientific innovation and technological development.

In general I take TA as promoting a much needed democratic culture of participation about the development of science and technology. Traditional political institutions and regulatory bodies may retain their politically legitimating function by mandating and coordinating these activities themselves. Alternatively, the organisation of social appraisal of technological change can stem directly from interested parties, thus building civil society as a powerful democratic location for social learning and deliberation.

Irrespective of the level of political institutionalisation, TA can however engage wider publics in the governance of stem cell innovation and, hopefully, contain the erosive risks of current framing efforts. In particular, through participatory and constructive TA, whether politically mandated or not, it may be possible to attain higher levels of accountability to the early efforts at translating stem cells into clinical applications.

Such exercises in technological forecasting and political anticipation are made necessary by the adversarial character of older controversies about embryonic research and early disputes about translational trajectories. Certainly, the platform-like character of stem cell technologies makes it problematic to anticipate where exactly and how stem cells will be used with respect to patients. But this, far from undermining the value of TA-

based governance, makes it even more urgent that we find ways to cope with inherent uncertainties in a way that is responsive to perceived social priorities and health-care needs. Only in this way can stem cell innovation attain the social robustness that is necessary for its steady development towards new cures for future patients.

Conclusion

The promise of stem cell medicine is a fascinating one, but the route to its fulfilment is still uncertain nonetheless. In this dissertation, I highlighted the contentious negotiations that engage relevant stakeholders in trying to position themselves as powerful actors with respect to stem cell clinical innovation.

In introducing my methodological outlook for the present dissertation, I described the way in which the explanatory potential of the co-productionist framework can be complemented by a philosophical account of deliberative democracy (see *supra*, chapter 1). I could thus avail myself of a hybrid bundle that, while maintaining a minimal and healthy degree of tension between its two components, provides a thick rendering of the discursive interactions that take place around biotechnology, and puts the analyst in the position to assess, normatively, the political quality of innovation trajectories. The field of social studies, indeed, seems to have recently engaged in similar theoretical projects, as testified by the so-called 'participatory turn' (Jasanoff 2003) in STS and technology assessment (TA). The issue of public engagement in science and in policy-making about science has thus generated a wealth of scholarly literature on these topics, bringing social and political scientists to interact with each other and with political philosophers, thus cutting across different disciplinary sectors.

As it emerged from my previous analyses, the current configuration of stem cell governance is mediated by discourses about clinical risk, quality and purity of cellular products, modes of material circulation for human stem cell lines and certification of pre-clinical and clinical knowledge. The overall picture is one of a still fluid regulatory

landscape, where no individual actor succeeded in gaining an absolute dominant position. As a consequence, due to regulatory loopholes, state-specific differences, public expectations about stem cell therapy and alternative framings of the clinical route to stem cell translation, diversity characterises current efforts at fulfilling the promise of stem cell research. The simultaneous presence of "contradictory voices and fragmented messages" (Baxter 2002, 828) marks the diverse field of stem cell innovation and governance, as revealed through my methodological outlook – one that, from the very beginning, gave prominence to the discursive constructions of policy-makers and innovators. What emerged is thus an unstable model of governance to cope with the scientific uncertainty and the clinical unpredictability of a field of innovation that, currently, is still under construction. I therefore stressed the way in which technical uncertainties about the biological behaviour of stem cell lines and indecisions about the clinical framing of stem cell therapies result in a discrepant regulatory regime. Furthermore, fractures and interruptions in the political order of stem cell clinical research have emerged across nation state borders as well. A traditionally reliable boundary of regulatory power, the latter appeared as being variously transgressed by alternative constructions of the innovation trajectory of stem cell science and practice.

The indecisions that surround the future application of stem cells to medicine are evident. On the one hand, stem cells therapies could be developed, and regulated, as new medicinal drugs. Industries and patent holders have a preference for this thread of translation for the obvious reason that standardising an individual stock of proprietary cells for its use as a pharmacological product, would straightforwardly allow the creation of revenues on the sale of such product for clinical applications. In the view of many, this model would encourage early investments in the clinical development of cell therapies by private companies and venture capital firms – investments that, so far, have been

minimal if compared to the amount of public spending on stem cell research and, furthermore, concentrated in very few investigational studies. Framing the development of stem cell therapies in a way that equates it to the development of a drug would therefore provide possible returns for the risky initial investments of private funders. Moreover, by the same token, a drug-like framing, we have seen, is functional to bring the field under the regulatory control of governmental agencies, thus putting them in a powerful position to steer and oversee the clinical development of stem cell applications. Many commentators argue however that, in this framing, commercial interests and patent thickets illegitimately capture the developmental dynamic of innovation in the field of stem cell research. Indeed, interpreting this regulatory configuration as a shared model of governance also captures the convergence of epistemic and moral commitments of scientists and regulators, as I have shown above. Controlled clinical trials, performed under the normative framework of internationally valid principles of human research ethics, thus represent a common ground for this particular framing to be implemented in practice: they assure a technical definition of risks in terms of cellular purity and absence of contamination, while leaving room for individual negotiations between certified experts as to the management of the complications that may arise in the course of clinical studies.

Blind spots nevertheless remain for other actors to criticise this framing. Some argue that the time- and resource-consuming stepwise process of CCTs actually stifles progress in the field, thus ultimately damaging patients who might benefit from innovative therapeutic approaches early on.

As a consequence, on the other pole with respect to the previous framing, we noticed the emergence of a different understanding about the way stem cells could and should be brought at the patient's bedside. Instead of articulating stem cells as

manufactured drugs, other stakeholders see them as natural products, whose safety profile, in specific therapeutic settings, is sufficiently stable to grant their direct administration to patients who require them. The source of revenue for practitioners of this kind of stem cell medicine does not come from the sale of cells themselves, but rather from the administration of a medical service, like in the case of surgery or other non-pharmacological medical procedures. This model of translation, as I have shown, relies on the regulatory gaps left open by the previous framing and on state-to-state political differences. Interested stakeholders, in this case, contend that such clinical procedures are scientifically unwarranted and thus ineffective, if not dangerous. Also in this case, commercial interests are used to discredit the reputation and the credibility of practising stem cell doctors. This contention carved a profound disciplinary as well as cultural divide between stem cell clinics physicians, on the one side, and stem cell scientists backed by regulatory agencies on the other. Again, the regulatory model appears to be shared between the latter and the former, and none of the involved actors seems to hold a position of absolute control over the initiatives of the other. Nonetheless, judiciary and political activities mediate continuous efforts at constructing regulatory supremacy.

Politics, it seems, lags behind the boisterous development of stem cell medicine through innovative practices and unproven treatments offered on an international medical market. In the case of stem cell translation, it thus seems that state initiatives are lacking their familiar ordering efficacy, and inevitably leave room for the articulation of a rather dispersed regulatory order. In truth, a more veridical interpretation of the role of politics in the emerging governance of stem cell clinical applications should see political actors as being on a par with other relevant stakeholders in trying to establish their ends onto this field of biomedical innovation. The state, in other words, should be understood

as an interested party in the development of stem cell innovation and not as a neutral mediator of the interests of others. It appeared from my previous analyses that states, through their legislative powers and bureaucratic endowments, push their own narratives about biomedical change through the intricate web of different framings and contrasting interests that forms the landscape of stem cell innovation[35]. What my account of the governance of early stem cell translation has shown, however, is that national policy-making has changed its nature with respect to the past decade. In the case of regulating stem cell derivation from embryonic and foetal material, state intervention was indeed responsive to precise industrial and political strategies that brought about severely controlled regulatory regimes (Gottweis, Salter, and Waldby 2009; Salter and Salter 2010; Salter and Faulkner 2011). However, when stem cell research started to translate to the clinic, a process that, as I showed, is still in its infancy, those strategies had to cope with the technical uncertainties and clinical novelty of the field, thus resulting in the comparably under-structured shared model of governance that I depicted in chapters 3.II and 4.

In the fifth chapter, drawing on those realisations, I have thus assessed this emerging regulatory order form a deliberative perspective. In so doing, I have suggested that a democratic polity incurs in risks of democratic erosion due to the current political configuration of stem cell translation. Therefore, I have articulated a few normative proposals as to the political stakes of innovative medicine and I had proposed institutionalised mechanism of stakeholder inclusion and citizens participation to cope with it. In so doing, I drew on participatory and constructive technology assessment

[35] This feature has been clarified in the work of political scientist Brian Salter and sociologist Alex Faulkner, who, within the interpretative framework of 'competition states' and 'developmental state' theory, insightfully described the agency of political actors as being oriented to the pursuit of national advantage and biotechnological hegemony (Salter 2007; Salter 2009; Salter and Salter 2010; Salter and Faulkner 2011).

techniques that may help align technological development with the expectations and interests of wider publics. Albeit imperfect and strongly sensitive to the context of their implementation, these techniques may represent a first move in the direction of a more accountable, and thus politically more stable translation of stem cells into valuable applications for mankind. To this aim, I have maintained, fostering a democratic culture of participation and inclusion appears to be an answer to the divisions that characterised the social environment of biotechnology in the last few decades.

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