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# REPROGRAMMING PLATFORMS. THE CO-PRODUCTION OF SCIENTIFIC AND GOVERNANCE INNOVATION IN TRANSLATIONAL INDUCED PLURIPOTENT STEM CELL RESEARCH

*Luca Marelli*

Matricola n. R09832

*Supervisor:* Prof. Giuseppe Testa

*Added supervisors:*

Prof. Andrew Webster
Prof. Sheila Jasanoff
Dr. Stefano Casola

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# Abstract

This dissertation charts the rise and articulation of induced Pluripotent Stem Cells (iPSCs) as a prominent translational technology, invested with high expectations to finally deliver the as yet mostly unfulfilled promise of stem cell research. In a field catalyzed by the therapeutic promise, iPSCs have been adopted for widespread translational efforts, in the areas of disease modeling, drug discovery and regenerative medicine, and have progressively positioned themselves, through the mobilization of several biomedical platforms, as a key resource of stem cell-based bioeconomies.

Specifically, drawing from extensive ethnographic fieldwork, this work targets distinct iPSC innovation pathways across the United States and the European Union, and conducts the analysis of distinct models of iPSC–based innovation implemented by three leading iPSC research organizations that have been spearheading translational iPSC research: the New York Stem Cell Foundation, the Harvard Stem Cell Institute, and the European Bank for induced Pluripotent Stem Cells – respectively, the largest stem cell research organization in the world; the largest private translational stem cell research institution in the United States; and one of the two flagship stem cell consortia launched in recent years at EU level.

Through a comparative approach, this dissertation explores the co-productive relationship between scientific and governance innovation, and probes the distinct ways in which some of the leading research institutions in the field design and implement governance arrangements and practices of standardization in order to harness the innovation potential of iPSC-based technologies. Furthermore, it accounts for the socio-political salience of these emerging institutional configurations, and traces the assembly of distinct constituencies claiming jurisdiction in this domain of biomedicine.

# Introduction

It was June 2006 when Japanese scientist Shinya Yamanaka, speaking at the 4th International Society for Stem Cell Research (ISSCR) annual meeting in Toronto, Ontario, reported the soon-to-be-published discovery (Takahashi and Yamanaka 2006) that induced expression of just four genes was enough to "reprogram" terminally differentiated murine adult cells to a state of pluripotency, yielding induced Pluripotent Stem Cells (iPSCs). Received as the pinnacle, and the point of synthesis (Stadtfeld and Hochedlinger 2010), of five decades of research into cellular development and cloning technologies[1], as well as in techniques for the establishment and maintenance of a pluripotent state in 'immortalized' cell lines[2], Yamanaka's announcement astounded as much as it inspired the packed audience reunited in Toronto. "We had the distinct feeling that we were witnessing a historic moment unfolding", a scientist attending the event recalled (field notes 2015). A year later, at the end of 2007, after a frenzy of attempts, Yamanaka's group, along with a pool of other leading stem cell labs, reported the derivation of iPSCs from human somatic cells (Takahashi et al. 2007; Yu et al. 2007; Park et al. 2008), thus paving the way to the portability of iPSCs technologies into the clinical domain. And it did not take long - a mere six years since his landmark 2006 publication - for Yamanaka to be awarded the utmost stamp of scientific recognition, the 2012 Nobel Prize in Physiology or Medicine (jointly with John Gurdon, for his own pioneering research on nuclear transplantation half a century earlier): not only did iPSCs rewrite chapters in biology textbooks; also - and

[1] See Briggs and King 1952, 1955; Gurdon 1962; Gurdon et al. 1975; Wilmut et al. 1997; Cowan et al. 2005.
[2] See Stevens and Little 1954; Kleinsmith and Pierce 1964; Evans and Kaufman 1981; Martin 1981; Thomson et al. 1998.

crucially - they were to open up "a whole new frontier of research into potential clinical applications" (Nobel Assembly 2012).

This dissertation is aimed at charting the rise and articulation of iPSCs as a prominent translational technology, invested with high expectations to finally deliver the as yet mostly unfulfilled promise of stem cell research (Wu and Hochedlinger 2011).

In a field catalyzed by the therapeutic promise, iPSCs have been swiftly heralded as the "holy grail" of stem cell technologies (Hauskeller and Weber 2011), and have consequently been adopted for widespread translational efforts, in the distinct, yet interlinked areas of disease modeling, drug discovery and regenerative medicine. In the study of human diseases, iPSCs are proving to be meaningful models to elucidate disease pathogenesis and progression (Han et al. 2011), since they allow to make genetic variation experimentally tractable, while also providing access to previously inaccessible cell types (e.g. neurons); on the therapeutic side, they have raised prospects for both drug screening, by enabling testing for drug efficacy and toxicity in a disease- and patient-relevant context (Engle and Puppala 2013), and the potential treatment of degenerative diseases, through replacement of affected cell types (Cyranoski 2014).

In light of these features, iPSC research has progressively positioned itself as a mainstay of advanced as well as developing bioeconomies and knowledge-based societies worldwide. Governmental agencies and private investors, in Western and Asian countries alike, have mobilized a large amount of material, financial and cognitive resources towards the establishment of state-of-the-art biomedical platforms (Keating and Cambrosio 2003), as well as bio-networks (Patra and Sleeboom-Faulkner 2009; Sleeboom-Faulkner and Patra 2011) operating on iPSC research at the transnational scale (e.g. Mikami 2014; Sleeboom-Faulkner and Hwang 2012; Thompson 2010, 2013; Zhang 2011). While iPSC research initiatives taking place in Japan stand out owing to sustained state-led efforts at primacy in the field (Mikami 2014), iPSC research platforms worldwide both collaborate and compete

in standardization practices aimed at stabilizing the field (Webster and Eriksson 2008; Webster 2013). Also, they strive to develop models of governance that could successfully advance desired framings of iPSC-based innovation, so as to gain competitive advantage in the distinct yet interlinking markets of scientific credibility, intellectual property rights, biomedical commodities and socio-political prestige (Salter 2013).

Against this momentous development, this dissertation intends to provide an insight into the dynamics of the innovation journey (Van de Ven et al. 1999) of iPSCs, as they evolved from being a novel technoscientific breakthrough at Takahashi and Yamanaka's bench at Kyoto University to being a widely circulating technology in research and clinical centers worldwide. Specifically, drawing from extensive ethnographic fieldwork, this work targets distinct iPSC innovation pathways across the United States (US) and the European Union (EU), two important political and geographical areas in which iPSC research has developed. The US in particular, owing to a longstanding primacy in biomedical innovation (Salter 2013), hold the lion share in terms of diffusion of this technology, as measured by the patented inventions filed for iPSCs since 2006 (Roberts et al. 2014).

More specifically, this dissertation conducts the analysis of distinct models of iPSC–based innovation implemented by three leading iPSC research organizations that have been spearheading translational iPSC research: the New York Stem Cell Foundation (henceforth: NYSCF), the Harvard Stem Cell Institute (henceforth: HSCI), and the European Bank for induced Pluripotent Stem Cells (henceforth: EBiSC) – respectively, the largest stem cell research organization in the world; the largest private translational stem cell research institution in the United States; and one of the two flagship stem cell consortia launched in recent years at EU level.

Japan – a country whose strong state commitment in translational iPSC research has even led to what Mikami (2014) designs as an ‘imaginary lock–in’ in science policy – would surely have warranted attention to broaden the scope of the analysis. However, the

ineludible logistic difficulties inherent in arranging an in–depth study of Japanese iPSC research (ranging from funding to the language barrier) made such option impracticable. Part of the follow up work of this dissertation will thus focus on analysis of Japanese iPSC research[3].

## 0.1 Adjusting the analytic gaze.

The choice of these *case studies*, the focus on these *organizations*, as well as the methodology adopted for my analysis: these are all relevant aspects of this work that warrant a preliminary clarification.

For one thing, the choice of these three case studies, HSCI, NYSCF and EBiSC, owe to their neglect in social sciences studies of stem cell innovation (contrary, for instance, to the equally relevant case of the California Institute for Regenerative Medicine (CIRM), extensively analyzed by Thompson (2013) and Benjamin (2013)), as well as to their relevance and profound impact in the field of iPSC research. In different ways that I elucidate in the course of the dissertation, all these three leading iPSC research centers have been playing a crucial role in shaping the standardization trajectory of iPSC–based innovation, and are thus privileged sites for analyzing the consolidation of the field.

Second, the choice of focusing on these organizations hinges on a twofold consideration, partially related to the methodology being adopted.

Consistent with a well–established stance developed in the field of Science and Technology Studies (henceforth: STS), in which this dissertation is firmly rooted, I maintain that biomedical innovation, far from solely owing to technical advances, has a strong normative component embedded into it. And the focus on these iPSC research centers – which represent a *meso*–level of analysis, in between the *micro*–level of individual iPSC research laboratories, and the *macro*–level of practices and regulations

[3] However, I have conducted a first inroad into Japanese stem cell research in a forthcoming co-authored paper revolving around the recent STAP scandal. See Meskus et al. forthcoming.

that play out at the national and supranational level and cut tangentially across the whole iPSC research field – is the one that, I contend, is best suited to capture *both* the epistemic and the normative import of iPSC research. For, on the one hand, what remains analytically invisible at the level of the individual stem cell laboratory is the *normativity* that steers research practices through a variety of governance mechanisms. On the other hand, what escapes the analytic gaze by focusing on institutional and diffused macro–structures is the nitty–gritty of experimental practices – one that, in shaping the *epistemic* and *technical* component of emerging technologies, undoubtedly represents as well a central aspect of biomedical innovation.

Specifically, to account for both these dynamics, in this dissertation I build on Keating and Cambrosio's notion of biomedical platforms (Keating and Cambrosio 2003) and deploy it within Jasanoff's co-productionist framework (Jasanoff 2004), to probe symmetrically the mutual constitution of *governance* and *epistemic standards* within the three leading iPSC research centers. Not only, by resorting to different strategies of standardization, these organizations pursue distinct paths to iPSC–based innovation. Also, they design and adopt distinctive models of governance, through which different constituencies advance different normative commitments and visions that they strive to materialize by means of iPSC research.

Building on this analysis, I then seek to bring to the fore questions of macro–order to which major endeavors in the life sciences inevitably led – especially in a time when human cells have been increasingly replacing coal and steel as the main threads in the fabric of economic development and the forging of new political identities. Hence, I probe the intimate connection that ties these models of iPSC–based innovation to the public sphere, tracing the assembly of distinct constituencies claiming jurisdiction in this domain of biomedicine and thereby enacting distinct 'constitutional' dispensations of the role of science within society (Jasanoff 2003).

## 0.2 Entering a field I never left. From project conception to empirical access and data collection.

In ways that go beyond my formal affiliation with the European School of Molecular Medicine (SEMM) at the European Institute of Oncology (IEO) in Milan, this project owes a lot to the setting in which it was conceived, took a tentative inception, gained momentum, and fully developed.

Since its conception in the late spring of 2012, the idea to provide an as yet unattempted cartography of the field of iPSC research needed the completion of some fundamental groundwork in order to develop into a full-fledged research project. In particular, aside from methodological fine-tuning and full immersion into relevant STS as well as scientific literature, a robust, first-hand knowledge of iPSC research practices was needed, if I were to gain a sufficient understanding of the key issues at stake so as to develop and refine my research questions prior to my entering the field of empirical enquiry. In that regard, the physical proximity with - when not outright embeddedness into - a leading biomedical institution proved to be a catalyzing factor to develop these enabling skills.

In particular, my supervisor's dual role as an STS scholar and biomedical scientist conducting cutting-edge iPSC research provided me with the perfect opportunity to match my intellectual aspirations with a sound preparatory work that helped me to familiarize with the bread and butter of iPSC research. From June 2012, I started what proved to be a year-long internship (lasting until August 2013, with a brief interruption from July to September 2012, when I took up a visiting teaching position in Hermeneutics and Post-Modern Philosophy at Saengtham College in Nakhon Pathom, Thailand), during which I regularly attended weekly group meetings in Giuseppe Testa's lab (henceforth: GT lab), and also devoted around 50% of my work time to work at the bench. Not only, as in Latour's famous preaching, was I to follow scientists. All of a sudden, in a way totally unforeseen just a few months before, I was acting as one of them.

While this experience would require an ethnographic account of its own (something beyond the scope of this dissertation), I am here going to limit myself to highlight its relevance for the subsequent part of my fieldwork.

First and foremost, the lab internship allowed me to get acquainted with the most widespread experimental practices occurring in a tissue culture facility – the physical place where the ontology of iPS cells is crafted in its materiality. While embedded in GT lab, my main task was indeed to provide assistance at first, and replacement soon thereafter, to some PhD students and a post-docs for the processes of iPSC derivation, culture, and expansion. Among the main tasks that I had to perform were daily media change, iPSC colonies selection and picking (this refers to the visual inspection and manual selection, through a needle and a pipette, of the best clusters of cells, i.e., those that have been fully reprogrammed to become *bona fide* pluripotent stem cells), iPSC colonies expansion, and formation and differentiation of embryoid bodies (i.e., spheroid structures derived from clusters of stem cells that, upon differentiation into the three germ layers, can provide a first proof-of-principle of their pluripotency). In doing so, I achieved experimental fluency in dealing with a number of different protocols, media and techniques.

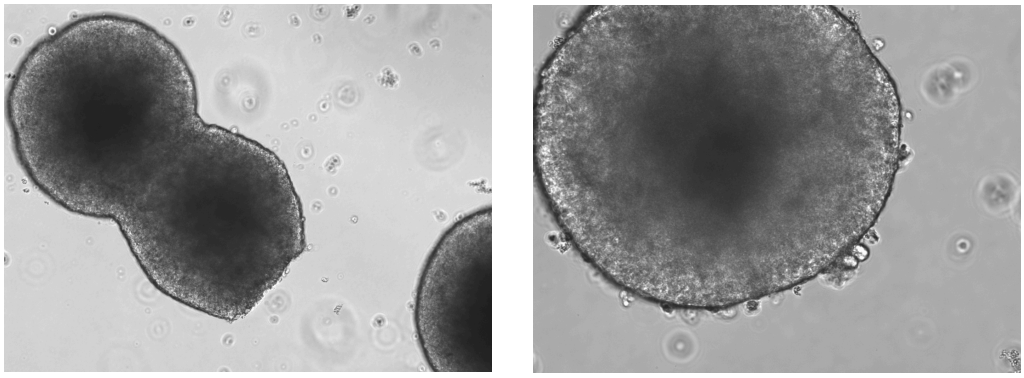


**Figure 1. Embryoid bodies formation. June 2013.**

Adjacent to this, and consistent with my position at the bottom of the hierarchical ladder within the lab (which often entails the involvement in riskier kinds of projects (see Knorr-Cetina 1999)), I was handed the attempts to test (in fall 2012) a new culture condition for the cells (a cheaper one compared to the one that was currently in use in the lab, and that

also required less hands-on time), and, most notably (in spring and summer 2013), to replicate a recently published protocol revolving around the modeling of human cortical development *in vitro* using induced pluripotent stem cells (Mariani et al. 2012). The replication attempt required intensive tinkering with both the cells and the equipment, and allowed me to familiarize with some of the widespread techniques in molecular biology, other than those commonly employed in culturing cells. Unsuccessful in the end, this endeavor allowed me to widen my perspective outside the confined walls of a tissue culture facility, as well to confront issues arising in the design and set up phase of experimental systems.

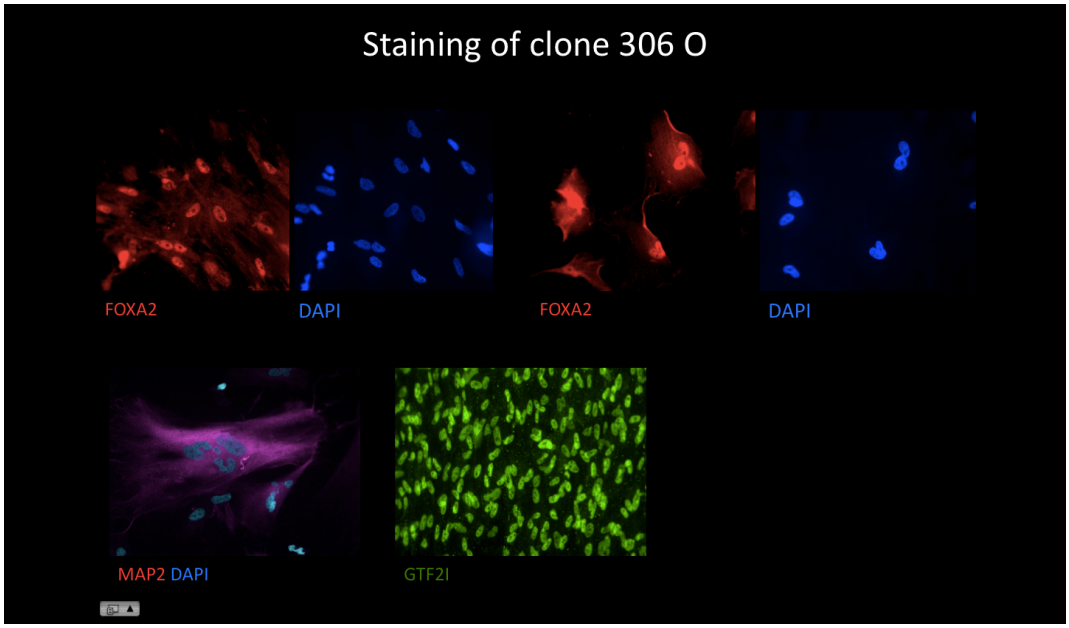



**Figure 2. EBs stainings. Slide from presentation given at GT lab meeting in July 2013.**

Overall, insofar as it provided me with a unique vista on iPSC research practices, the knowledge that I gained throughout such intensive - and, at times, rather daunting - internship was enabling for the development of my project for a number of reasons. First, it helped to redefine and adjust my research questions, bringing issues of standardization at the center of my focus. Second, it also played an important part in the choice of the unit of analysis to adopt: iPSC *platforms* rather than individual labs, so as to better account for the macro-political normativity accompanying standardization practices, something which remains analytically invisible within the walls of the lab. Third - and for the very same

reason - it prompted a reassessment of the qualitative techniques to employ in my fieldwork, where - with the notable exception of attendance to closed doors meeting at the iPS Core Facility and to meetings of Kevin Eggan's group at HSCI - I gave preference to interviews rather than observations of the work of the scientists – since acquaintance with the latter had already being achieved while in GT lab. Fourth, it primed my understanding of the situation I was going to encounter in the field, thus facilitating and streamlining the process of data acquisition.

As such, and contrary to my first descent to the tissue culture facility at the first floor of my own building at the Ifom-Ieo Campus, the moment I entered the iPS Core Facility at the Harvard Stem Cell Institute in September 2013 - the 'official' beginning of my fieldwork - did not feel at all as awkward. It rather felt as if I never left the lab.

### 0.3 Methodological note on fieldwork arrangements.

A year-long fellowship in the Program on Science, Technology and Society, directed by Prof. Sheila Jasanoff, at the John F. Kennedy School of Government at Harvard University provided me with the perfect springboard for my HSCI fieldwork. Affiliation to the same institution I was going to study greatly helped in streamlining the process of data acquisition.

In particular, through connections already established by my supervisor with the leader of the iPS Core facility, Chad Cowan, I was able to set up multiple visits to the Core. Furthermore, other than holding frequent meetings with the head of the facility, from October 2013 to October 2014 I was able to attend close–door meetings that took place among participants to its various projects, and also conduct separate semi–structured interviews with the main actors involved.

While at Harvard, adopting snowball techniques I was also able to reach out to various HSCI scientists, working in various departments and affiliated hospitals.

From October to December 2013, I also attended weekly lab meetings at a leading iPSC lab directed by Kevin Eggan. During that time, I could attend two meetings devoted entirely to standardization. During these meetings, the normal routine of individual projects' presentation was suspended, and the whole lab, led by the P.I., engaged in discussions on how to better standardize lab protocols. This experience, coupled with my previous experience at the GT lab (and my ongoing attendance of its weekly lab meetings), helped me to reinforce my understanding of the multi-faceted standardization landscape of iPSC research.

As for NYSCF, protracted negotiations were eventually conducive to set up a visit to the facilities in April 2014. The visit took a full day, involved both observations of scientists at work, informal discussions at lunchtime and during coffee breaks, and semi-structured interviews with relevant members of the organization. In particular, the visit allowed me to become acquainted with their main laboratory equipment, the robotic system for iPSC derivation, expansion and differentiation (the Global Stem Cell Array, described here in detail in chapter 4). During the visit, I established connections that allowed me to set up further interviews with members of the organization, and to get access, upon my return to New York City in October 2014, in order to attend NYSCF's annual translational stem cell conference, to closed-door events related to the conference.

Upon my return to Italy, in August 2014, I started making arrangements for my EBiSC fieldwork. My supervisor's membership in EBiSC Ethical Advisory Board (EAB), and support from the Center of Ethics and Law in the Life Sciences (CELLS) at Hannover University (from February to August 2015), a partner in the EBiSC consortium, facilitated access to the organization. Furthermore, a visiting period at the Science and Technology Studies Unit (SATSU) at the University of York, directed by Prof. Andrew Webster, in

April and May 2015 represented an ideal platform for conducting fieldwork in the UK, where a number of EBiSC partners were based.

Finally, a methodological overview, with a complete list of the interviews conducted and the relevant meetings attended, can be found at the end of the dissertation (see Appendix I).

## 0.4 Structure of the dissertation.

The dissertation sets out by providing a contextualization for the rise of translational iPSC research, and the emergence and consolidation of translational iPSC research platforms. To this purpose, chapter 1 is aimed at exploring the scope and significance of the phenomenon of clinical translation, for, I contend, the push to accelerate biomedical innovation (i.e. the translation of laboratory findings into tangible therapeutic products) has greatly informed the developmental trajectory of iPSCs. In particular, I focus on the narratives and metaphors through which the push to translation is articulated, and look at how these discursive practices are materialized into strategic programs, governance reforms, and novel material and epistemic cultures that have significantly altered, in the last decade, the landscape of biomedical research.

Chapter 2 provides an overview of the iPSC research landscape, so as to acquaint the reader with its jargon, concepts and practices. I thus sketch here the core features of the iPSC research platform, and trace the key junctures of the iPSC developmental trajectory, while providing a brief overview of some of the main issues that have been confronted by stem cell laboratories worldwide to standardize iPSCs. In addition, I analyze the main epistemic tenets of iPSC–based disease modeling, reconstruct the narratives and expectations around iPSCs' therapeutic potential, and provide a closer look at the use of iPSCs in clinical research.

In chapter 3, I expound my analytic approach, developed for the analysis of my case studies, which builds on the notion of *biomedical platforms* proposed by Peter Keating and Alberto Cambrosio (2003) and the *co–productionist* program advanced by Sheila Jasanoff (2004). Specifically, in this chapter I trace the distinction between two distinct ways of applying the co–productionist lens to the analysis of biomedical platforms (see also Marelli and Testa forthcoming). First, I argue that biomedical platforms propel what I term the *endogenous co-production* of scientific innovation and regimes of governance, through the adoption of mutually constitutive standardization and governance practices. Second, I contend that reprogramming-based platforms are also conspicuous examples of a higher, meta-level of 'reprogramming', through which platforms are sculpted by and in turn re-shape their broader socio-political context, and that I propose as an *exogenous* form of *co-production*. Finally, I argue that both kinds of co–productionist accounts are needed in order to capture the dynamics of innovation revolving around biomedical platforms in contemporary biomedical research, as well as their relevant socio–political implications.

The second part of the dissertation deals with the empirical analysis of my case studies. Chapter 4 sets out by outlining the most significant junctures in the chain of events leading to the current policy configuration of the field of stem cell research. Next, it expounds how they have been brought to bear on the establishment of a leading iPSC research institution in the US, the New York Stem Cell Foundation, a venture philanthropy–backed organization distinctively advancing a disruptive innovation approach to translational iPSC research.

Chapter 5 attends to the progressive entrenchment of stem cell research at a bastion of American academic research, Harvard University, by focusing on the establishment of the Harvard Stem Cell Institute. While similarly advancing a translational stem cell research agenda, HSCI maintains in many significant respects a different approach from the one

articulated by NYSCF, one aimed at sustaining – rather than disrupting – established research practices in the field of stem cell research.

Chapter 6 accounts for how translational iPSC research is enrolled and mobilized in the process of renegotiation of the 'European' economic – but also political – identity. The chapter focuses on the revealing case study of the European Bank for induced Pluripotent Stem Cells (EBiSC), established in 2014 within the framework of the Innovative Medicines Initiative (IMI), a Public Private Partnership – the world's largest – between the European Commission and the European Federation of Pharmaceutical Industry and Associations (EFPIA). Here, I expound how, through EBiSC's endeavor, the stabilization of a new and enticing field of research is co-produced along with the structuring of a significant portion of the European science policy.

Finally, in the conclusions I make explicit what had been left implicit in the previous chapters. Accordingly, I trace comparisons between the three iPSC research platforms analyzed in the dissertation, and I bring to the fore the way they distinctively embody different visions concerning the role that ought to be played by stem cell research within the broader socio–economic–political order.

# Chapter 1. Accelerating Biomedical Innovation: the Translational Turn in Biomedicine[1]

In a 2003 Policy Forum in *Science*, then NIH director Elias Zerhouni announced the launch of the 'NIH Roadmap' (Zerhouni 2003). Comprising a series of initiatives intended to "transform the nation's medical research capabilities and speed the translation of discoveries from the bench to the bedside" (NIH Press Release 2007), the NIH Roadmap marks the beginning of a 'translational turn' in biomedicine. From that moment, clinical translation emerged as a new field of sociotechnical practice – one that acquired significance well beyond the confined walls of laboratory and clinical facilities. 'Clinical translation' has since become a widely circulating buzzword, a touchstone – not immune from controversy (Maienschein et al. 2008, Jogalekar 2011) – for biomedical, patients' and policy communities alike. As it has been said, "translational research means different things to different people, but it seems important to almost everyone" (Woolf 2008).

The present chapter is aimed at exploring the scope and significance of the phenomenon of clinical translation, focusing in particular on its discursive embodiments that convey and recast the interests, expectations and commitments of a broad array of communities within and around biomedical research and, at the same time, re–produce those stances into

[1] The reflections presented in this chapter owe in a significant way to a collaborative project on clinical translation undertaken with colleagues at INSERM (France), University of Vienna (Austria), and Harvard Medical School (USA). In particular, I draw here extensively from a co–authored, equally contributed paper, in review at the moment of writing, quoted as Aarden, Blasimme, Holloway and Marelli (forthcoming). In preparing this chapter, I also benefited from participation at two events where I presented parts of the present work: first, a workshop on 'Making sense of clinical translation: ethical, regulatory and policy challenges for Europe and the US', held at the Brocher Foundation in Hermance, Geneva, on May 18–19, 2015, which I have co–organized along with the aforementioned colleagues; second, a panel on "Politics and Ethics of Translational Medicine", held at the Science and Democracy Network 14th Annual Meeting, that took place at Harvard University on June 25–27, 2015.

strategic programs, governance reforms, and novel material and epistemic cultures in biomedicine.

The underlying assumption that informs this chapter is that it would not be possible to appreciate the noticeable excitement raised in biomedical constituencies by the advent of iPSCs, as well as to attend to the trajectory taken by their standardization pathways (Webster 2013), without contextualizing their emergence and stabilization within the underlying conceptual and normative framework of *clinical translation*. Since the onset of the new millennium, following the first sequencing of the entire human genome (Lander et al. 2001; Venter et al. 2001) and the launch of the NIH Roadmap in 2003 (Zerhouni 2003), a vast array of socio–technical practices revolving around biomedicine has been moulded, and profoundly reconfigured, by the imperative to "accelerate translation", i.e. the clinical application of scientific discoveries. Not only does the push to translation performs a central role in shaping the current evolution of the biomedical enterprise writ large. In the case of iPSC–based technologies, I argue (and will show in the next chapter), it has pervasively informed the dynamics of their innovation journey (Van de Ven et al. 1999), steering their development from an emerging technoscientific breakthrough at Takahashi and Yamanaka's bench at Kyoto University to a widely adopted technology in clinical and research centers worldwide.

Providing an overview of the phenomenon of clinical translation represents, accordingly, an obvious entry point for – one could even possibly say an obligatory passage point (Callon 1986) into – the rest of the present dissertation.

For one thing, the momentous development of iPSC research, as I will expound at greater length in the next chapter, has been greatly informed by the *translational ethos* that upholds "the implicit value that science that can be translated into results is the best science, and everything else is second–tier" (Maienschein et al. 2008). Not only the greater translational potential that *induced* pluripotent stem cells carry vis–à–vis their embryonically or clonally derived counterparts (see chapter 2) has significantly

streamlined the rapid uptake of iPSC–based technologies by laboratories worldwide. Also, their standardization trajectory – from the quest for reprogramming methods geared to augment the efficiency and completeness of reprogramming, while preserving genomic integrity so as to avoid tumorigenicity upon injection in the body; to the development of characterization assays enabling a shift from a qualitative to a digitized assessment of pluripotency, thus allowing the handling of a higher number of cell lines; to the attempt to devise consenting procedures for donors geared to facilitate the commercialization of research findings – has been shaped by the intent, from the part of scientists, industrial representatives and investors alike, to greatly accelerate their clinical deployment, be it in the form of cell–based therapeutics or as tools for modeling diseases and testing for new compounds.

Secondly, the establishment and consolidation of leading iPSC research platforms in the United States and the European Union, whose detailed characterization constitutes the core of the present work, has been significantly influenced by the translational imperative. From the New York Stem Cell Foundation, to the Harvard Stem Cell Institute, to the European Bank for induced Pluripotent Stem Cells, each and every one of these leading iPSC research platforms variously resort – to both set forth their objectives, and carve out for themselves a space of public legitimacy – to the framings, norms and expectations encoded in the translational discourse. In particular, whether it is by developing innovative modes of governance, the blurring of entrenched disciplinary boundaries, or the creation of synergies among public and private actors, they all assume upon themselves what constitutes the kernel of the translational trope, namely, the mandate to accelerate the pace of (stem cell–based) biomedical innovation.

Against this backdrop, the present chapter is devoted to sketching the contours of the conceptual and normative framework of clinical translation. Specifically, in section (1.1), I trace the origins of the translational turn in biomedicine in the framing of biomedical innovation first explicitly advanced by the NIH Roadmap in 2003, and argue that, in its

broader connotation[2], clinical translation increasingly represents the underlying organizing principle of contemporary biomedical research. Next, in section (1.2), I show that clinical translation presents itself primarily as a discursive phenomenon, and contend that the extensive use of rhetorical practices and metaphors – to which the translational discourse abundantly resorts – to characterize the obstacles hindering biomedical innovation has a profound impact in the way both the ontology and the agenda of clinical translation is defined. In particular, these metaphors point to what, drawing from Aarden, Blasimme, Holloway and Marelli (forthcoming), can be designed as the *translational lag narrative*, i.e. the idea that the pace of clinical innovation lags behind that of scientific discoveries, and should be accelerated accordingly. It is this narrative that, so I argue, acts as a potent driver for the enactment of profound scientific and organizational reconfigurations in biomedicine (section 1.3). Also, it advances distinct normative agendas and collectively held visions of desirable socio–political orders to be attained by means of accelerated biomedical innovation (section 1.4).

Throughout the chapter, I thus aim to bring to the fore some of the widespread normative commitments and expectations underpinning the standardization trajectory of iPSCs, as well as the establishment and consolidation of iPSC research platforms, so as to lay the groundwork for the analysis conducted in the following chapters.

## 1.1 The translational turn in biomedicine.

In its current form, clinical translation finds its inception, following in the footsteps of the first sequencing of the human genome, in the launch, spearheaded by then NIH Director Elias Zerhouni (a Bush administration appointee), of the NIH Roadmap. The

[2] As noted by Vignola–Gagnè (2013), the notion of clinical translation maintains many different connotations, and is equally characterzied as a 'discipline', 'experimental practice' as well as 'political agenda'. The analytic rendering of this notion proposed in this chapter (see section 1.1) is aimed at distinguishing, within its semantic breadth, a narrow connotation of the term, as a specific *disciplinary* approach in biomedical research, from a broader connotation referring to its character as an overarching *framework* structuring a broad variety of practices in contemporary biomedicine.

result of a year–long reflection involving scientific as well as lay constituencies ranging from academia to governmental agencies and the private sector, the NIH Roadmap set out from the realization that, notwithstanding the ever–increasing epistemic and cultural authority commanded by the life sciences at the onset of the 21st Century, "critical scientific gaps" (Zerhouni 2003) preventing the streamlined transition from discovery to application still had to be addressed. In Zerhouni's own words, while the sequencing of the entire human genome, announced in June 2000, triggered visions of unprecedented scientific and medical opportunities, it also created "a series of challenges that will redefine the ways that medical research is conducted and, ultimately, how research leads to improvements in health" (Zerhouni 2003). As noted in Aarden, Blasimme, Holloway and Marelli (forthcoming):

> *In an unexpected twist of positivist optimism, all of a sudden, progress ceased to appear as the natural output of scientific ingenuity. Even more importantly, for the first time a discrepancy was detected: that between the "unprecedented acceleration of scientific discovery" and the lagging pace of "clinical translation" (Zerhouni 2003). The latter expression began to circulate and came to designate an area of unfulfilled promise – one that called for urgent remediation. According to the new vision sketched by the roadmap, the relation between discovery and delivery had to be re–engineered. "Roadblocks" had to be removed (ibid.)*.

The relevance of the NIH Roadmap should not be underestimated. Since its launch, clinical translation, first introduced as a concept in the 1990s (Encyclopædia Britannica), came to be widely recognized as a scientific and social priority, to be vigorously pursued by creating the conditions to streamline the delivery of new therapies onto the market and into the clinic. In particular, the consolidation of the translational field occurred through two conjoined, but in fact distinct trajectories. On the one hand, clinical translation emerged, out of a process of professionalization, as an *autonomous discipline*, possessing peculiar methodologies and objects of enquiry (Cambrosio et al. 2006a), as well as

dedicated research and funding institutions (e.g., The National Center for Advancing Translational Science (NCATS), established in 2011 within the NIH), journals (e.g., the *American Journal of Translational Research*, *Translational Research*, *Science Translational Medicine*, *the Journal of Translational Medicine*, *Clinical and Translational Medicine*, *Stem Cells Translational Medicine*, etc.)[3] and career patterns (see Nathan 2002). On the other hand – and most notably for the purposes of the present dissertation – the impetus towards translation became both a widespread *ethos* (Maienschein et al. 2008) and *style of reasoning*, introducing "new criteria determining what counted as the solution of a problem"[4] (Crombie 1994; see also Hacking 1985, 1994, 2004, 2012; and Boem 2015), that came to underpin policy and funding programs while organizing a broad variety of research practices as well as collective priorities in biomedicine (Vignola–Gagné 2013).

Therefore, in this second broader connotation, clinical translation not only represents the latest stage in the incremental realignment of biology and medicine that characterizes the advent and consolidation of biomedicine itself (Cambrosio et al. 2006b), but also marks a fundamental moment of sociotechnical transition, one that significantly reconfigures, not without resistance from some biomedical constituencies (Jogalekar 2011[5]), the approaches, scope, and practices of the life sciences, while bringing forth profound changes in biomedicine's own epistemic culture (Knorr–Cetina 1999). As such, the translational enterprise is geared to have a structuring effect on the whole biomedical research enterprise. Contextually to enacting profound changes in biomedicine's contexts of

[3] Journals dedicated to translation started to appear in the early 2000s and have been listed in Thomson Reuters' Journal Citation Report only since 2009.

[4] In particular, as the empirical chapters of this dissertation will attest, in translationally–oriented endeavors emphasis has progressively shied away from traditional forms of peer recognition (i.e., the peer–reviewed publication) towards therapeutic innovation.

[5] For instance, notes Jogalekar, "what is wrong is that translational research is being seen as a panacea that will address the flagging rate of new biomedical advances. The thinking seems to declare that if only more people were given more money and deliberately focused on direct application, we would suddenly see a windfall of new therapies against disease. This thinking suffers from two major problems. The first is that history is not really on the side of translational research. Most inventions and practical applications of science and technology which we take for granted have come not from people sitting in a room trying to invent new things, but as fortuitous offshoots of curiosity-driven research. […]The second important problem with translational research is that it puts the cart before the horse. First come the ideas, then come the applications."

discovery and justification (Reichenbach 1938), i.e. in the ways new experimental hypotheses are generated, and regarded as methodologically sound, it sets forth and widely disseminates, as argued (and decried) by Maienschein and colleagues (2008), those *constitutive* and *epistemic values* (Longino 1990; Daston 1992; Daston and Gallison 2007) definitory of contemporary 'good biomedical science', while also reshaping social relations in biomedicine's underpinning institutional context.

Accordingly – it ought to be noted – clinical translation so understood maintains a difference in kind with respect to other novel approaches in the biosciences, such as 'personalized' or 'precision' medicine, that are oftentimes spearheaded by strategic initiatives of institutional connotation, similar in nature to the NIH Roadmap (see, e.g., the *Personalised Medicine for the European Citizen* (Look 2012), and the Precision Medicine Initiative in the US (NIH 2015)). Whilst notions such as 'precision' and 'personalized' medicine are meant to define new practices and programs of intervention, oftentimes said to be re–envisioning no less than the future of medicine itself (see, e.g. NIH 2015), they still owe in significant ways to the overarching framework of clinical translation (whose main tenets I trace below), thus configuring themselves as specific *means* to achieve the broader translational objective of shortening the distance from discovery to application. For, in the spirit of the latter, such approaches are meant to devise *outcome–driven* programs of intervention intended to maximize the clinical actionability of post–genomics technologies and discoveries[6], and to produce new types of biomedical knowledge more amenable to clinical translation[7].

[6] For instance, precision medicine's prevention and treatment strategies that take individual variability into account (Collins and Varmus 2015) are seen as a way to "to *leverage* advances in genomics [...] and health information technology" in order "to *accelerate* our understanding of disease onset and progression, treatment response, and health outcomes" (NIH 2015, italics mine).

[7] As stated in the *Personalised Medicine for the European Citizen* report: "Personalised medicine is a *new approach* to classifying, understanding, treating and preventing disease based on data and information on individual biological and environmental differences. It seeks to integrate data on the entire dynamic biological makeup of each individual as well as the environmental and lifestyle factors that interface with this makeup to generate a complex, individual phenotype. Using this information, models can be generated to identify the *most appropriate* healthcare choices, from treatment to prevention, in individual citizens." (ESF 2012, italics mine)

In what follows, I thus aim to expound the twofold significance of clinical translation as a *conceptual and normative framework* that, while it crystallizes a multiplicity of discourses on the problems faced by contemporary biomedical research into the narrative and interpretive schema of the *translational lag* (i.e., the notion that the pace of clinical innovation lags behind that of scientific discovery), at the same time reproduces and performs the stances coming from a broad variety of constituencies into strategic programs, governance reforms, and novel material cultures in biomedicine, all geared to *accelerate* the pace of *biomedical innovation*.

## 1.2 Articulating clinical translation: the *translational lag narrative*.

As an actor category mobilized in biomedical as well as policy settings, clinical translation is typically articulated according to a widespread conceptual dichotomy, and is imagined to operate as either a linear (unidirectional) pathway or as an iterative process, in the space defined by the clinical and laboratory poles, of which it would itself occupy the middle ground[8].

In its *linear framing*, most famously epitomized by the "bench–to–the–bedside" metaphor, clinical translation is conceptualized as the effort to bring breakthroughs in basic biomedical sciences to bear on clinical outcomes, through distinct translational phases corresponding to identified 'translational blocks' that have to be overcome. In particular, commentators have identified the T1 phase concerning the production and commercialization of new drugs, devices, and treatment options for patients, and the T2 phase concerning the reorganization of systems of care so as to effectively accommodate the new treatments in the day–to–day clinical practice (Sung et al 2003; Woolf 2008). More to the point, the T2 model shares with T1 the intuition that our ability to understand human biology and pathology is unmatched by our current capacity to alleviate the burden

[8] While these framings can be (largely) compatible, commentators typically draw from, and give prominence to, either one or the other to conceptualize clinical translation.

of disease on people's life. However, T2 is not concerned with accelerating the pace of the transition from discovery to invention – as T1 arguably does. Rather, this other model has to do with the dissemination of innovation and the fair allocation of medical resources to the sick population. While these two models can be seen as compatible, and in fact coexistent in the process of bringing basic research to bear on clinical outcomes, T2 has been at times articulated in rather oppositional terms with respect to T1. For example, it has been noticed that "[s]cientific discoveries and spectacular new devices are more fascinating to the public and more lucrative for industry, [whereas it is t]he betterment of health [that] should dictate priorities in health research" (Woolf 2008). Such a public health–oriented approach to understanding the meaning of translation, albeit having been circulating for more than a decade now, has however exerted a smaller influence on the overall articulation of the problem of translation.

In its *iterative framing*, on the other hand, translation is understood as a two–way traffic between the lab and the clinic, whereby concepts are brought from the laboratory into the clinic, and insights generated from clinical observations are recursively brought to bear on laboratory practices. Only through the close–hand, synergistic, and iterative interaction of the biological and clinical poles of research, so the argument goes, can rapid development and commercialization of new therapeutic products be achieved.

However, in spite of their differences, what both these conceptualizations entail, and reinforce, is a dichotomous and compartimentalized perspective on the process of knowledge–translation, whereby translation implies a clear–cut distinction between two domains, and an in–between hiatus to be filled up by translational programs and practices, operating either in a linear or iterative way.

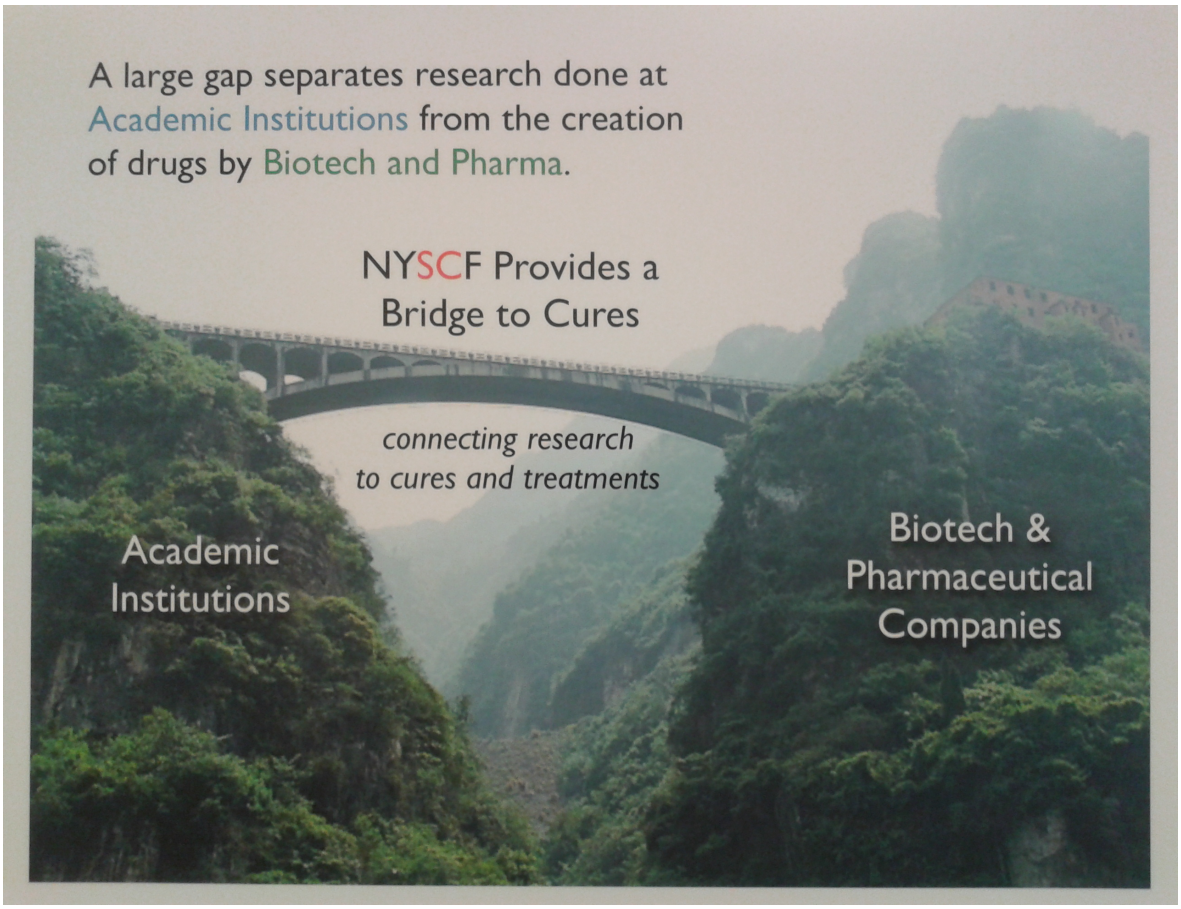
Such conceptualizations owes, in many respects, to the *discursive premises* onto which clinical translation is deeply rooted. Indeed, the translational turn is being heavily propelled through a proliferation of linguistic formations and rhetorical metaphors that, as Vignola–Gagné persuasively observes, "solicit adhesion to an agenda by emphasizing the

threat of a purported alternative" (Vignola–Gagné 2013). Scouring scientific publications and policy documents, one thus finds patent "cliffs" to be overcome, "gaps" to be "bridged", and "bottlenecks" and "roadblocks" to be removed. Conversely, one witnesses the acclaim of "roadmaps", "catalysts" and "pathfinders" promising to move knowledge across the most formidable obstacle of all, the "valley of death" hampering the clinical and commercial uptake of scientific findings. Far from just playing an ancillary role in advancing and giving urgency to the translational research program, these discursive practices define the very *ontology* of the translational paradigm itself. The specific locution of gaps, valleys, pipelines, pathways and roadblocks imbues translation with a spatial and temporal dimension, and advance a well–defined *framing of the problems* facing biomedicine, while shaping accordingly the translational research agenda.

Urgency to overcome the purported dichotomy between the "bench" and the "bedside" is perhaps most vividly evoked by the representation that what separates them is, in fact, a "valley of death" (see e.g. Butler 2008). What this metaphor suggests is the idea that major hindrances are situated on the way from laboratory to clinic, or from discovery to application. Thus, the way to address them is to find a way to bring the poles of the lab and the clinic closer together. As such, the translational agenda has its solution built into the problem definition. If the problem with clinical application of biomedical knowledge is the opening (and widening) of a space between bench and bedside, this space–between becomes a site of intervention – and opportunity – for translationally–oriented programs and practices.

Most importantly, all these metaphors converge to construct a *translational lag narrative* (Aarden, Blasimme, Holloway and Marelli forthcoming): the notion that the pace of clinical innovation lags behind that of scientific discovery. Constant breakthroughs in laboratory research and technological advances are thought to be producing, at an increasing rate, possibilities for new treatments. What the lag narrative portrays, though, is that too few of them are developed into tangible treatments, and those of them that do take

far too long to reach patients. Accordingly, what the narrative advocates as means to bridge the gap are *innovation* – which refers to strategies of turning knowledge into things, biomedical insights into therapeutics – and *acceleration* – which refers to strategies of doing so faster. As a consequence, since the launch of the NIH Roadmap, proposals to solve the problem have constantly focused on closing the gap by accelerating and innovating: the need to *accelerate* biomedical *innovation* has thus become a widely repeated *mantra* (Maienschein et al. 2008), with that of clinical translation coming to embody a prominent instantiation of the late modern imaginary of accelerated techno–scientific progress (Rosa and Scheuerman 2009; Rosa 2013; see also Virilio 1997).



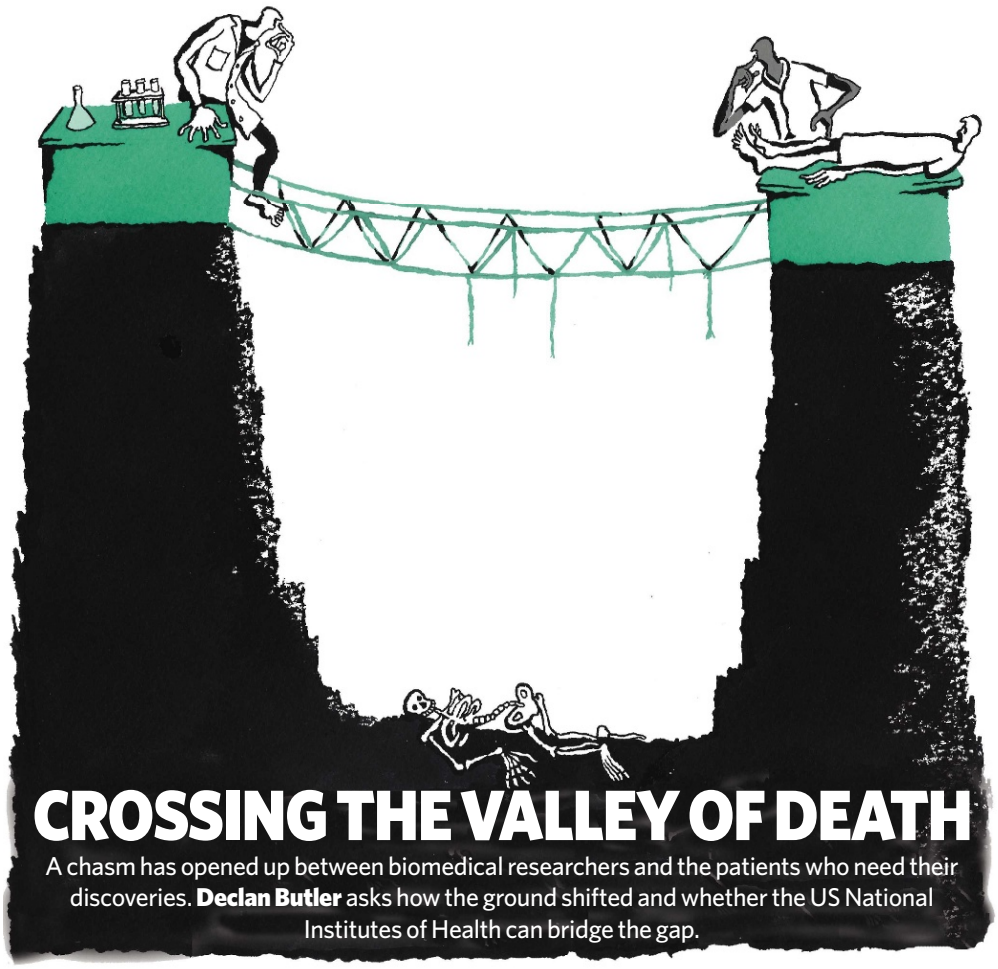



**Figure 3. Different visual renderings of the 'valley of death'. (1a) Photo taken in NYSCF's laboratory. (1b) Butler 2008**

As many of such kind, the translational lag narrative relies heavily on the *mobilization of the future* as justification for investments in programs aimed at repairing the lag and innovation strategies geared to promissory and highly speculative projects filled with uncertainty. This mobilization is enacted through the construction and performance of expectations that encode visions of future orders to be attained as well as dystopic projections – as the varied renderings of the valley metaphor attest – of unwanted consequences to be avoided (Brown and Michael 2003; Borup et al. 2006; Jasanoff and Kim 2009, 2015). At the same time, the framing of translational projects as functional and conducive to desirable sociotechnical futures is co–constructed along the 'translation' of wants into needs, or what may be desirable to achieve in the future into what is actually

needed. Accordingly, advancing a framing of the present in terms of scarcity, the discourses revolving around translation are pervaded by a rhetoric of acceleration (Rosa 2013). As noted by Aarden, Blasimme, Holloway and Marelli (forthcoming):

> *The clinical translation of knowledge into medical innovation embodies one of the contemporary incarnations of the modern myth of endless progress. At a careful examination, however, it appears to be driven equally by the hope of development as by the dread of stagnation. The more ideals of enhanced biomedical possibilities take shape, roughing out a future of prosperity and health, the more present forms and values assume the semblance of impediments. This trait explains why a narrative of acceleration dominates the discursive landscape of clinical translation. Hence, in the quest for clinical translation, the promise of development incorporates one of radical change.*

The idea that clinical application does not follow naturally from the sheer accumulation of biological knowledge constitutes the stable core of the lag narrative and of its associated metaphors. This "story line" (Hajer 2006) is associated with the idea that the transition from discovery to innovation needs to be dramatically accelerated.

Historically, the sense of urgency built into the translational discourse, rather than the outcome of a predominant master narrative stemming from a well–defined socio–technical world, emerged, in recent decades, from the crystallization and convergence of several strands of critique and concerns about the production and application of medical knowledge.

In the 1980s, HIV–AIDS patient–advocacy groups played an important role in expanding and accelerating access to experimental drugs. Confronting an entrenched medical elitism, they successfully strived for recognition and scientific credibility (Epstein 1996; Dresser 2001; Daemmrich 2004) paving the way to the establishment of new patient–centered biomedical collectives (Rabeharisoa and Bourret 2009) often endowed

with the capacity to significantly impact the orientation (and acceleration) of research programs concerning their diseases (Rabeharisoa and Callon 2004). At the policy level, the thrust towards translation emerged as the byproduct of (top–down) legislative actions undertaken in the 1980s, aimed at forging closer ties between academia and industry in order to speed up the commercial uptake of "basic" scientific discoveries (Guston 2000) – with the Bayh–Dole Act (1980) most famously spearheading such initiatives (Cooper 2008; Loewenberg 2009). In parallel, emphasis on the creation of closer academy–industry collaborations was heightened by industrial actors themselves, willing to access previously untapped academic innovation as a mean to reverse an enduring and widely publicized productivity crisis (Stinchcomb 2009; Stevens et al. 2011). Finally, as far as experimental practices themselves are concerned, the affirmation of the translational paradigm is rooted in developments occurring in cancer research in the 1990s, aimed at creating synergies between (the then segregated) laboratory and clinical types of research, which resulted in the consolidation of a translational interface that was de facto non–existent a few decades before (Cambrosio et al. 2006a).

Even though it was not until the 2000s, after the first sequencing of the human genomes and through the undertaking of initiatives such as the NIH Roadmap, that clinical translation started becoming the shibboleth that it is today, its process of consolidation owes in many significant respects to the multiplicity of its historical roots. Stemming from these distinct perspectives, that around translation emerged indeed as a *multi–layered narrative.* In it, a variety of technical and lay discourses – ranging from those revolving around the productivity crisis in the pharmaceutical industry, to those encoded in strategic programs advanced by governmental agencies, to participatory claims advanced by patient advocacy groups, etc. –converge onto the idea that clinical innovation is stagnating and should be geared up towards the accelerated production of tangible outputs. As it has been noted, "although different, these interpretations [of translation] are not mutually exclusive. Rather, they reflect different priorities for achieving a common goal" (Encyclopædia

Britannica). Thus, while the kernel of the translational trope has remained considerably stable over the years, its perduring solidity owes to the multiplicity of the intertwined discursive strands of which it is composed – in a way similar to what Meloni and Testa observe with regard to the "blurring of meanings as a critical asset" for the structuration of the field of epigenomics (Meloni and Testa 2014). As argued in that regard by Aarden, Blasimme, Holloway and Marelli (forthcoming):

> *Far from being a precisely defined space of sociotechnical interaction, clinical translation is thus best understood as a landscape onto which different discursive articulations of the [translational] lag struggle to find some sort of correspondence with social and political reality. Translation, so characterized, is not understandable independently of the multiple discursive practices that constitute and travel its extension. [...] Analysis shall therefore do justice to the multiplicity of meanings, expectations, values and regulatory commitments that are currently being traded around the metaphors and scenarios that translation evokes. Each technical world produces its own version of the valley metaphor, as in an effort to claim epistemic authority and social credibility over the project of translation itself. The proliferation of metaphors in this area corresponds to the multiplicity of technical discourses that coexist on the territory of clinical translation.*

Within most biomedical constituencies, and beyond, that of the *translational lag* arguably became, in recent times, the most prominent conceptual and normative framework to both *represent* the maladies ailing biomedicine, and to *orient* the deployment of material and cognitive resources in a variety of programs aimed at addressing them. Having provided an overview of the discourses and conceptual coordinates of clinical translation, in the next section I focus on its sociotechnical performativity, i.e. on how clinical translation re–produces those stances into strategic programs, regulatory reforms, and novel material cultures within and around biomedicine.

## 1.3 The manifold performativities of clinical translation.

Scholars in the social sciences and the humanities have variously interrogated, and critically addressed, the manifold sociotechnical transformations instigated by clinical translation, as well as their implications for biomedicine and society.

The thrust towards translation has been variously framed as a vivid manifestation of a rampant neoliberal capitalism, and seen as geared to a privatization of biomedical goods (Kahn 2014), an increased capitalization and globalization of the life sciences (Sunder–Rajan and Leonelli 2013), and the generation of biovalue (Waldby 2002) through exploitative forms of clinical labor (Cooper and Waldby 2014). Moreover, the translational rush is seen as reinforcing entrenched geopolitical asymmetries, through the establishment of bio–networks operating across different countries (Patra and Sleeboom–Faulkner 2009; Sleeboom–Faulkner and Patra, 2011). In a similar fashion, scholars within the sociology of medicine have shown how a "neoliberal corporate bias" plays out in upholding industry's interests in drug development and (de)regulation carried out in the name of accelerated translation (Lewis and Abraham 2001; Abraham 2002, 2008), while others have questioned what may get "lost in translation" (i.e., which kinds of science are no longer considered to be legitimate uses of public and private resources), vis–à–vis the emergence of a "translational ethos", advanced by what they call the research–medical–industrial enterprise writ large (Maienschein et al. 2008). Other strands of analysis have attended to the bioconstitutional transformations (Jasanoff 2011) fostered by efforts at translation, through a redistribution of power and agency among actors and 'stakeholders' involved in the biomedical enterprise, in a way conducive to a redefinition of the scope and boundaries of citizenship on a national (Benjamin 2013) and global scale (Sunder Rajan 2011).

Lastly, Aarden, Blasimme, Holloway and Marelli (forthcoming) propose a topographic analysis aimed at charting how the discursive practices and metaphors revolving around

translation are articulated in a variety of sociotechnical worlds while retaining a distinctive capacity to perform the co–production of multiple epistemic and normative orders (Jasanoff 2004). In particular, the latter approach is geared to address the shortcomings of the aforementioned analytic perspectives, that, in spite of the distinct explanatory pathways they articulate, tend to similarly reify specific explanatory categories (such as corporate bias, neoliberal capitalism, etc.) and posit them as static, stable and pre–defined *explanans* of clinical translation (Dussauge, Helgesson and Lee 2015). As such, these approaches fail to account for the multiplicity of transformations instigated by the translational discourse in the domain of biomedical research, and for the broader reconfigurations it triggers in the socio–political landscape.

In particular, Aarden, Blasimme, Holloway and Marelli (forthcoming) identify four domains in which distinct articulations of the lag narrative, each highlighting diverse sets of problems hampering the smooth translation of scientific knowledge into tangible clinical outputs, propel profound socio–technical reconfigurations within and around biomedicine. These different, often connected, but not necessarily convergent perspectives casting distinct *diagnoses* of the maladies affecting the biomedical enterprise points to: (i) scientific, (ii) regulatory, (iii) ethical, and (iv) organizational impediments as major obstacles to be overcome so as to foster clinical translation. More to the point for our present discussion, two of these translational discourses, those revolving around the *scientific* and *organizational* hindrances slowing down the effective translation of novel biomedical insights, perform a key function in shaping iPSC research with its attending epistemology, as well as in propelling reconfigurations in its underpinning organizational arrangements. Accordingly, in what follows I briefly sketch the conceptual and rhetorical perimeters of these discourses, before analyzing, in the following chapters, how they are brought to bear on iPSC research practice and its underpinning institutional configurations.

(i) Scientific impediments.

A common thread in the discourse on translation points to obstacles in knowledge–flow as a major impediment to the transition from discovery to clinical application. A first, popular version of this narrative centers on the conventional *division of scientific labor* as a major epistemic hindrance for clinical translation. Traditionally, the production of scientific knowledge has been structured around disciplines with a high degree of specialization. However, notwithstanding the manifold advances witnessed in the last decades in the life sciences, so the discourse goes, this paradigm has been showing signs of wear. Not only has a 'siloed' approach to research, based on the experimental apparatuses of highly segregated disciplines, being challenged, and proved inadequate, by the advent of the so called 'big data biology' with its panoply of new 'omics technologies (Stevens 2013; Hood and Rowen 2013; Ratti 2015). Moreover, such approach has lead to major issues, such as the experimental reproducibility (or lack thereof) of scientific knowledge and its material inscriptions (Latour 1986), as they are made to move from the laboratory to the clinical domain to be transformed into fungible, clinically actionable (Nelson et al. 2013) products (Begley and Ellis 2012). As argued by Garret Fitzgerald, director of the Institute of Translational Medicine and Therapeutics at the University of Pennsylvania, in an op–ed published in *Nature* in 2010 and devoted to the difficulties facing pharmaceutical research in the transition from the pre–clinical to the clinical phase of experimentation:

> *Too many steps are pursued in specialist isolation, in both academia and industry. Too few people can bridge the translational and interdisciplinary divides. This has led to crucial and expensive mistakes in phase II of drug development — when there is often a failure to see an impact on efficacy, a propensity to ignore risks, or a danger of making errors in dose selection for phase III.*

Accordingly, such narrative has in recent years fed into an imagination of a future science that has fewer boundaries and moves towards the thorough interweaving, and seamless integration, of the diverse material and epistemic components of the life sciences.

Moreover, increased efforts at removing the obstacles in knowledge–flow, and creating synergies among the diverse phases of the biomedical innovation pipeline, have begin to *blur the boundaries between research and treatment*, whereby the two previously distinct – and diachronically ordered – moments become aligned within the same biomedical platforms (Keating and Cambrosio 2003). As attested by the advent of new sociotechnical practices revolving around novel technologies with their accompanying social innovations, such as direct–to–consumer (DTC) genetic testing (Parthasarathy 2010; Curnutte and Testa 2012), iPSC–based technologies (Saha and Hurlbut 2011; Marelli and Testa forthcoming), and body–on–chip models (The Economist 2015; Bhatia and Ingber 2014; Maschmeyer et al. 2015) – to name but a few relevant examples –, the seemingly solid division between research and treatment falls away as the clinic becomes a primary site of innovation. Thus, epistemically, every patient can, at the same time, become a source and a target of extrapolation (Germain 2013), whereby real–time data and the clinical knowledge generated from her/his lived–experience (Canguilhem 1978) maintain a key function for both design and interpretation of experiments in the laboratory (Coleman and Dreesen 2009), which, in turn, can be more swiftly translated into clinically–relevant knowledge. From a socio–political perspective, the advent of practices such as DTC genetic testing propels the emergence of new sites in the production of both biological and clinical knowledge, while reconfiguring the role of the patient–consumer as a prominent actor – in fact a work provider (Cooper and Waldby 2014) – in biomedical innovation (Curnutte and Testa 2012).

How these aspects play out in the development of iPSC–based technologies is what I address in the next chapter.

(ii) Organizational hindrances and reconfigurations.

Another prominent account of translation frames the latter as a domain that demands an organizational gearshift. The mandate to accelerate translation, so a widespread narrative goes, requires, in parallel to removing the obstacles in knowledge–flow, profound institutional transformations in biomedical research, leading to what has been framed as the co–production of the life sciences' epistemic content and institutional arrangements (Cambrosio et al. 2014).

Notably, the development of *new modes of governance* is often seen as a necessary prerequisite to both foster the delivery of new therapies onto the market and into the clinic (Salter 2013) and to accompany the introduction of novel, and potentially disruptive, technologies so as to "bring them in harmony with human existence" (Nowotny and Testa 2010). Moreover, in the name of accelerated translation, advocacy organizations coalesce around specific diseases and areas of enquiry (e.g., see Rabeharisoa and Bourret 2009); research collaborations, spanning institutional and national boundaries (e.g., see Sleebom–Faulkner and Patra 2011), are established, along with state–sponsored programs aimed at fostering competitiveness in enticing new (bio)economic territories, in advanced and in developing countries alike (Salter 2013).

Among the problems identified in the 'organizational discourse' around translation is the lack of support for truly innovative research, aimed at forging new paths of inquiry. This feature is mainly manifested in the policy of funding agencies, which, according to this narrative, tend to privilege research projects showing the most solid foundations over those with a path–breaking potential (Ledford 2012). This feature of contemporary funding programs has thus propelled the *intervention of new actors*, such as philanthropic organizations (Bartek 2014; Marelli and Testa forthcoming), eager to support high return, high risk projects that would normally not receive funding or attention by risk–adverse funding institutions (Johnson 2010). In turn – as I address at a fine–grained level of

analysis in Chapter 4, focusing on the revealing case study of NYSCF – the increasing involvement of new constituencies in the steering of biomedical research entails a privatization of the agenda setting prerogatives. As the latter move under the control of the private sector, they are subject to little or no public oversight, in a potentially costly trade–off between innovation and public governance of controversial yet highly promising fields of research (Krimsky 2007; Thompson 2013; Broad 2014).

Moreover, overcoming the disciplinary separations described above requires adapting the structure of scientific communities to novel epistemic needs. Under the translational paradigm, "the research teams of the future [are imagined to] look and feel vastly different from their predecessors" (Zerhouni 2003). In particular, *trans–disciplinary and trans–departmental collaborations*, aimed at addressing research questions going beyond entrenched disciplinary confines, have altered, in significant ways, the traditional landscape of biomedical research. Chapter 5, presenting a detailed account of the creation and consolidation of HSCI, analyzes one of the most relevant examples of such reconfigurations, occurring at a bastion of academic research in the US, Harvard University.

A further layer of the organizational diagnosis for the stagnating rate of translation has to do with the allegedly scarce level of *public–private partnership* (PPP) in the biomedical sciences. The efficient translation of basic knowledge into therapeutic outputs, so the argument goes, would benefit from a closer collaboration between academia and private actors, such as small biotechnology companies, venture capital and the pharmaceutical industry. Accordingly, chapter 6 focuses on a prime instantiation of the thrust towards trans–institutional collaborations, represented by the establishment, in 2008, of the Innovative Medicine Initiative (IMI) (Goldman 2012). The latter can count on joint yearly endowments from the European Commission and from the European Association of Pharmaceutical Industries and Associations (Efpia) and is the world's largest PPP in the

life sciences. Very much in line with the core of the translational narrative, IMI's mission is to "speed up the development of, and patient access to, innovative medicines, particularly in areas where there is an unmet medical or social need" (IMI 2014).

Crucially, these kinds of organizational reconfigurations aim at breaking new paths of discovery and innovation, but also have a broader, if less explicit impact. As I address in greater details in the following chapters, the re–organization of research instigated by the translational paradigm reaches beyond the organizational outlook of research teams. Translation–oriented endeavors bring about a redistribution of agency and power between different groups of stakeholders; propel the emergence and consolidation of innovative biomedical platforms (Keating and Cambrosio 2003), thus reconfiguring the roles and functions performed by the lab, the clinic, and the market in the biomedical research landscape; and, on a broader scale, redefine national priorities and collectively held representations of national futures (Jasanoff and Kim 2009, 2015).

## 1.4 Conclusions. The socio–political relevance of clinical translation.

In the first part of this chapter, I have touched upon the defining features of the discourse revolving around translation, identifying in the *translational lag narrative* the kernel of the conceptual and normative framework it advances, while, in the second part, I have accounted for its performativity in propelling novel sociotechnical configurations and reconfigurations in biomedicine. While certainly not exhaustive – something that would have been beyond the scope of the present work –, this overview serves the purpose of highlighting the significance of the translational turn in biomedicine. From the moment when, in 2003, the NIH Roadmap crystallizes the stances coming from a broad variety of communities into a well–defined schema to interpret and address the shortcomings of the present configurations of biomedical research, clinical translation, i.e. the faster clinical and market delivery of new therapies, has been increasingly envisioned as the ultimate

organizing principle of present–day scientific discovery, In this perspective, translation appears as the *regulative ideal* to which a disparate set of activities, from research to ethical oversight, from scientific organization to national science policy, must conform.

Moreover, not only does the translational discourse provide the interpretive lenses for identifying the hindrances to biomedical innovation, and a rationale, as well as a *bauplan,* for devising programs intended to address them, but it also acts performatively to materialize, through its envisioned reframing of the biomedical research enterprise, visions of desirable futures and normative stances concerning social and political order and the collective good.

As the distinct strands of the translational discourse attest, around translation coalesce distinct commitments and expectations advanced by a broad variety of constituencies. From pharmaceutical industries envisioning a future of increased profit–maximization beckoning them from beyond the valley of death, to governments of advanced and emerging economies alike embracing the narrative of accelerated biomedical innovation as they strive to preserve, or challenge, leadership positions in global knowledge–based markets; from private capital–backed foundations leveraging on the states' budgetary constraints in dire times of austerity, to assert a more prominent role in the steering of emerging technologies and fields of research, to biomedical communities increasingly envisioning their endeavors through the conceptual lenses, borrowed from the economic life, of "higher throughput" and "scaleable production": all these different instantiations of the thrust toward translation attest how the latter, far from merely revolving around the streamlined delivery of therapeutic outputs, is also a potent vehicle for advancing a number of distinct normative agendas and collectively held visions of desirable socio–political orders (Jasanoff and Kim 2015) to be attained by means of accelerated biomedical innovation.

In its *universalizing* aspiration – accelerating the clinical application of scientific discoveries – clinical tranlsation thus remains a *particular* and *situated* phenomenon,

which is continuously rearticulated in practice at a variety of sites, from boards of directors in multinational corporations and philanthropic organizations, to governmental science policy offices. A fundamental aim of the present work, accordingly, is to analyze how the diverse platforms, and the diverse constituencies they represent, re–articulate clinical translation in a variety of ways to fit their diverse normative commitments, or, differently put, how translation redefines, in distinct ways according to its different framings and practical implementations, the constitutional position of science within society (Jasanoff 2003).

# Chapter 2. Assembling the iPSC Research Platform

*The remarkable discovery of iPSCs by Takahashi and Yamanaka may be the molecular equivalent of the discovery of antibiotics and vaccines in the last century.*

Wu and Hochedlinger, Nature Cell Biology 2011

*I think it's the whole field of stem cells to be accelerated at a tremendous speed. 1998: hESCs. 2006: iPSCs. 2007: human iPSCs. Six years later Yamanaka wins the Nobel Prize… Well, it gave everyone the idea that 'bang bang', in a couple of years we'll be way forward… Everyone wants to be the first, to be the first to produce the first tangible results.*

Interview with stem cell scientist

As attested by the Nobel Assembly in their October 2012 press release announcing the award of the Nobel Prize to Shinya Yamanaka, whilst straddling research-oriented and application-driven (Carrier and Nordmann 2011) epistemic cultures (Saha and Hurlbut 2011), the field of iPSC research has built momentum, and fuelled expectations, in anticipating the realization of its clinical potential. In a field catalyzed by the therapeutic promise, iPSCs have been heralded as the "holy grail" of stem cell technologies, endowed with the capacity to finally deliver the latter's as yet mostly unfulfilled promise (Wu and Hochedlinger 2011; Hauskeller and Weber 2011). For this reason, iPSC–based technologies have been swiftly adopted for widespread translational efforts, in the distinct, yet interlinked areas of disease modeling, drug discovery and regenerative medicine.

How these developments have occurred, on the backdrop of a widespread thrust in biomedicine towards the acceleration of clinical translation, analyzed in the previous chapter, is what I am going to expound in this chapter of the dissertation. More to the point, I will proceed as follows.

First, in section (2.1) I sketch the core features of the iPSC research platform (Keating and Cambrosio 2003), and trace the key junctures of the iPSC developmental trajectory. In doing so, I provide a brief overview of some key issues that had - and in some respects still have - to be confronted by stem cell laboratories worldwide to tame the unruliness of these novel biomedical entities and standardize accordingly their material ontology. Next (section 2.2), I analyze the main epistemic tenets of iPSC–based disease modeling, and highlight how the former are brought to bear on the letter's translational deployment. Then, in section (2.3) I reconstruct the narratives and expectations around iPSCs' therapeutic potential. Finally, in section (2.4) I provide a closer look at the use of iPSCs in clinical research. In particular, rather than focusing on their development as *therapeutic products* for regenerative purposes, I mainly devote my attention to their usage as *translational tools* in drug discovery, i.e. as models for testing for new compounds. This choice is motivated by the fact that the platforms whose analysis constitutes the core of this dissertation are, in various degrees, similarly geared to the development of *iPSC–derived* (pharmaceutical) treatments, rather than *iPSC–based* (regenerative) therapies.

As its overarching aim, this chapters intends to provide an overview of the iPSC research landscape, so as to acquaint the reader with the jargon, concepts and practices of iPSC research, thus laying the groundwork for the empirical analysis conducted in the following parts of this dissertation.

## 2.1 Assembling the "core" of the iPSC research platform.

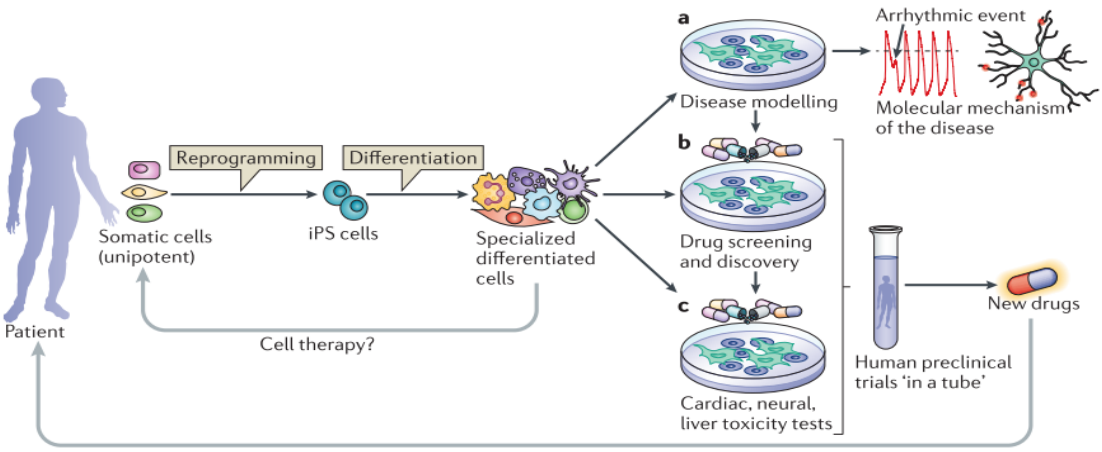



**Figure 4. The iPSC research "pipeline". From Bellin et al., *Nat Rev Mol Cell Biol* 2012**

Figure 1 provides a synopsis of the different "steps" of the iPSC research "pipeline", that constitute the *core* of the iPSC research platform (Keating and Cambrosio 2003). Schematically put, it can be described as follows. Following obtainment of informed consent from donors, somatic cells (typically skin or, since more recently, blood cells (Loh et al. 2010)) are harvested through a biopsy or blood procurement from patients and healthy "controls". Then, through a variety of methods, they are "reprogrammed" into iPSCs, expanded, and then differentiated into the relevant cell types (sometimes, as in the case of neurons, otherwise experimentally inaccessible), carrying the precise genetic mutation(s) of pathological relevance.

Differentiated cells, along with iPSCs themselves, are then used as *in vitro* models to provide insights into the molecular mechanisms underpinning disease. They can also be employed to conduct screenings for new compounds, while also allowing toxicity testing in a physiologically–relevant context. Differentiated cells can also potentially be used as cell–based therapeutics for regenerative purposes, through the replacement of affected cell types.

The assemblage of the iPSC research platform, described here in its essential features, has required significant "investments in form" (Thévenot 1984) from the part of different

biomedical communities. As iPSCs burst onto the biomedical scene, a number of issues pertaining to their standardization had to be confronted to turn them into a viable translational technology. In what follows, I account for some of the most relevant among them. Purpose of this brief review is not to provide an exhaustive analysis of iPSCs standardization, but rather to bring to the fore some of the issues that, at some key junctures of their standardization trajectories, had to be confronted by iPSC research platforms worldwide.

(i) Tissue samples procurement:

The standardization of the "upstream part" of iPSCs research has increasingly been perceived as an important goal for the stabilization of the field. In particular, it becomes an essential requirement for translating iPSCs into commercializable therapies (Grskovic et al. 2011).

A first important step in this regard concerns the recruitment of patients. Access to a broad patient population has been seen as a major, and at times indispensable, asset for pursuing research with iPSCs. In particular, large academic institutions with affiliated hospitals, with an institutional review board (IRB) process in place for collecting patient samples, are deemed as having a "strategic advantage" in collecting tissues and producing iPSCs (Grskovic et al. 2011). Accordingly, emphasis – especially from commercial actors – has been put in establishing linkages with such organizations, patient advocacy groups, academic clinicians and clinics that treat such patients, as well as in developing participatory platforms to enroll patients (REF.). The narrative revolving around the "moral duty" (Caplan 1984; Harris 2005) or the incentives to participate in research, either for altruistic reasons or purported personal benefits, has played a significant part in mobilizing the patients' broad endorsement and participation in iPSCs research (Dasgupta et al. 2014).

In the second place, especially following the entrance into the field of pharmaceutical corporations, worried about potential hindrances to the commercialization of research findings, the importance of standardizing consenting procedure has risen to the fore. As a the CEO of a company involved in iPSCs research noted:

> *At the moment, the problem is not making iPSC, it is the procurement. The delays are upstream. You do the collaboration, you work on the cell lines, get some nice things, then go out to the OTT, and you discover that the initial consent is not in line with the commercialization! That's why pharma […] is very interested in standardizing the upstream part.*
>
> Interview with CEO of an iPSC research company

To this end, a number of different consenting strategies, geared to ensure the streamlined circulation of research findings, have been developed, from "broad, one–time consents", to consent templates reflecting "an intention for sustained interactions with participants in select circumstances about the ongoing uses of their coded specimens" (Lowenthal et al. 2012).

(ii) Reprogramming methods:

Standardization of reprogramming technologies has been one of the single most important aspects concerning the stabilization of iPSC research practices. The development of improved reprogramming technologies, initially consisting in retroviral transduction of the reprogramming factors, has proceeded at a steady pace, programmatically driven by the intent to accelerate the clinical translation of iPSCs. In 2009, Jamie Thomson's group at the University of Wisconsin reported the successful reprogramming of human fibroblasts by a single transfection with episomal vectors (Yu et al. 2009), a technology later improved by Yamanaka's lab (Okita et al. 2011); the same year, Japanese researchers devised a reprogramming method based on the usage of Sendai virus (Fusaki et al. 2009);

while, a year later, Derrick Rossi's group at the Harvard Stem Cell Institute reported the conception of a reprogramming technology based on synthetic modified mRNA (Warren et al. 2010).

While taking different approaches, these methods were similarly geared to maximize the efficiency (i.e. the number of iPSCs generated per somatic input cell), and success rate (i.e. the percentage of samples for which iPSCs emerged) of reprogramming – in order to increase its yield – as well as to ensure the non–integration of reprogramming genes in the host genome, so as to avoid the risk of tumorigenicity upon injection of iPSC–derived cells into the human body.

Having being commercialized worldwide through readily available and widely used reagents and kits, these methods have rapidly become the mainstays of reprogramming technologies, whose choice of usage, as highlighted by a recent comparative study (Schlaeger et al. 2014), hinges on each platform's particular requirements (such as reliability in iPSCs derivation, need to reduce workload of generating iPSCs, amenability to automation, employment in GMP facilities).

(iii) Pluripotency assessment and iPSCs characterization:

Another key aspect concerning the standardization of iPSC research practice revolves around the development of techniques for the assessment of the defining feature of this entire field of research, i.e. the *pluripotency* of reprogrammed stem cell lines. More to the point, a general trend in the field has been to move from *qualitative* to *quantitative* and *digitized* assays, which in turn are meant to facilitate the development of, and their integration into, automated robotic technologies.

A first important evolution – still very much underway at the time of writing – has occurred in the practices and techniques of pluripotent stem cells' selection. Fully reprogrammed (and hence *bona fide* pluripotent) stem cells are typically grown in a colony–like shape, visually evaluated by experienced scientists, and manually "picked" in

order to be expanded (while non–reprogrammed, non pluripotent cells are discarded). As one scientific publication describes the procedure (Muller et al.2012):

> *"Visual inspection and manual selection of "good" from "ugly" looking colonies probably remains the most under-appreciated yet most important control instrument for pluripotent quality assessment, used every day in hPSC labs worldwide. Development of the expertise to decide which colonies to pick and which to discard requires apprenticeship with experienced researchers and is difficult to operationalize.*

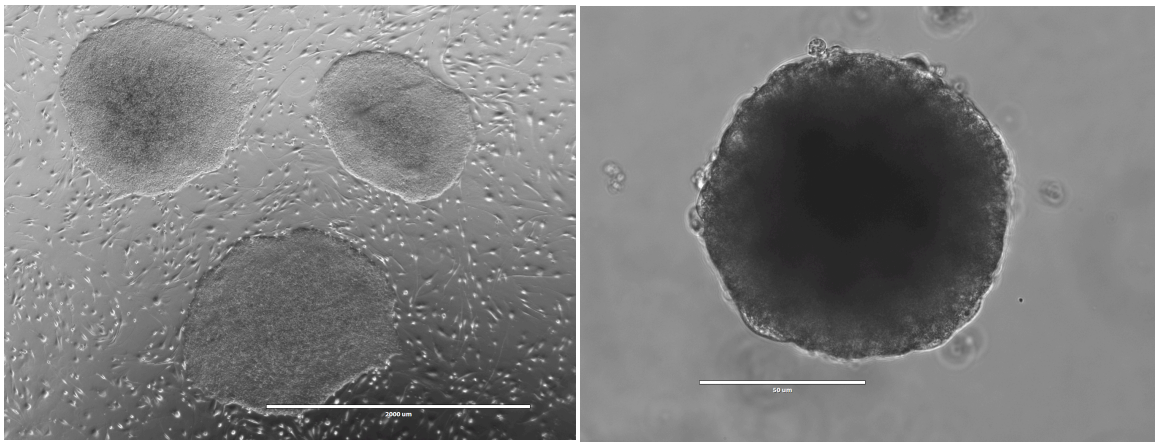


**Figure 5. Colonies of iPSCs (photo by LM)**

In fact, under the thrust to increase the *throughput* of cell lines (the biologists' jargon used to define productivity), the last few years have witnessed the progressive introduction of bio–imaging technologies that perform the *digitization* of the visually–assessed morphological parameters defining pluripotency (e.g., the shape of colonies, their growth rate, their rate of shape-changing) through their quantification into a discreet, binary signal (whereby the presence/absence of a single biomarker readout is taken as proxy for pluripotency, see e.g. Paull et al. 2015)[1]. Aimed at "flushing out" tacit knowledge (Keating

[1] The term *digital* is used here in a twofold connotation. First, as a *datum* amenable to be processed by means of bio-informatic technologies. Second, as a binary category (yes/no), and thus opposed to analog, i.e. something that allows for indefinite gradation (e.g. degrees of) . As noted by Germain (2013): "A digital watch, for instance, tells us the time in a single and definite way: there are not different ways of reading the watch to learn about the time, and one will not get more

et al. 1999) from the process of pluripotent colony selection, these novel technologies – an account of which constitute salient parts of chapters 4 and 5 – are envisioned to enable the scale up from experimental systems to systems suitable for industrial production, i.e. "from systems that are still returning knowledge through their instability and need for skill, to reliable, highly quality–controlled processes" (Fisher 2012).

For the same reasons – streamlining the process of iPSC derivation, and enabling a marked and otherwise unattainable increase in the yield of cell lines, in order to enroll iPSCs in circuits of higher curative and economic return, such as pharmaceutical research – the methods of iPSCs characterization[2] have themselves undergone a processes of quantification.

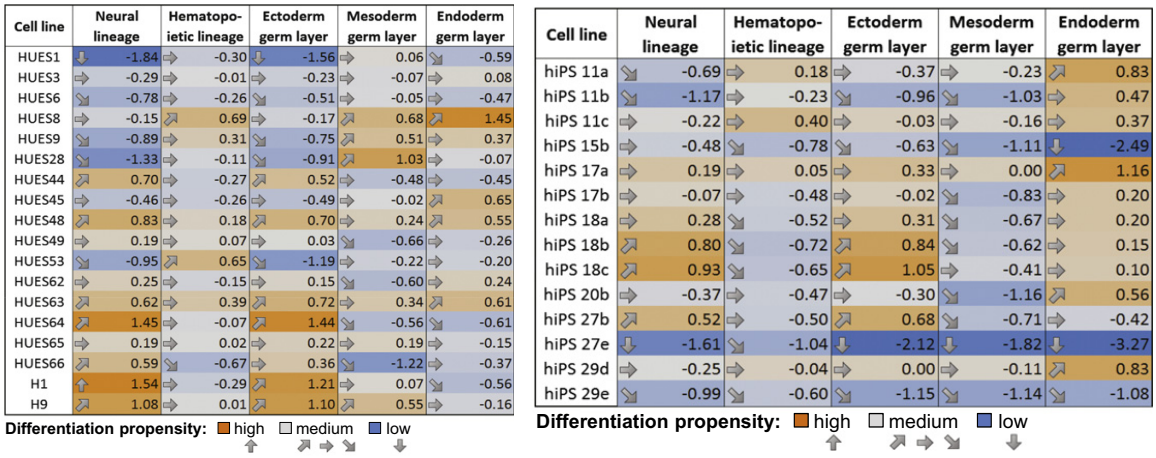
Since very early on in the experimental life of iPSCs, a major issue that had to be confronted was the comparability with hESCs, whereby, note Christine Hauskeller and Susanne Weber (2011), "the pluripotency of iPS cells need[ed] to be checked against the "normal" pluripotency of hES cells". Quite rapidly, the equal potency of hESC and hiPSC was established by striking "a balance between feasibility and epistemic power" (Germain 2013), and resorting to what was considered, at the time, "the most robust and ethically permissible standard" (Lensch et al. 2007) for pluripotency assessment, namely the formation of teratomas (usually benign tumours displaying tissues of the three germ layers) in immunodeficient experimental rodents (Park et al. 2008).

However, in spite of its status as the "gold standard" for pluripotency assessment (Park et al. 2008; ISCBI 2009), the teratoma assay presents some notable pitfalls, being hardly standardizable, expensive and time-consuming (Gropp et al. 2012). For these reasons, calls within the scientific community have gradually mounted (see e.g. Buta et al. 2013) for its

information by looking at it more closely. In other words, it is straightforward to say whether two watches are giving the same time. A gauge, by contrast, is analog (between any two points on the gauge is always another one), and in practice there is no saying that two measurements are the same (would they still be the same under a magnifier?)."

[2] Explain Marti and colleagues (2013): "Characterization of pluripotent stem cells is required for the registration of stem cell lines and allows for an impartial and objective comparison of the results obtained when generating multiple lines. It is therefore crucial to establish specific, fast and reliable protocols to detect the hallmarks of pluripotency**".**

replacement with *quantified in vitro* assays, that measure relevant DNA methylation profiles and gene expression levels. Insofar as they provide a remedy to these shortcomings, new technologies, such as recently developed 'PluriTest' (Müller et al. 2011) or 'Scorecard' (Bock et al. 2011), ,have been progressively adopted by laboratories worldwide and have been increasingly replacing the standard teratoma assay. Establishing a standard reference map for pluripotency assessment, an assay like the Scorecard presents the added advantage of predicting the differentiation potential of iPSC lines (i.e., their amenability to differentiation into a specific lineage), thus providing the level of specificity and detail – unattainable through the qualitative teratoma assay – that supports its application in a wide range of experimental procedures (Bock et al. 2011).



| Cell line | Neural lineage | Hematopo-ietic lineage | Ectoderm germ layer | Mesoderm germ layer | Endoderm germ layer |
|---|---|---|---|---|---|
| HUES1 | -1.84 | -0.30 | -1.56 | 0.06 | -0.59 |
| HUES3 | -0.29 | -0.01 | -0.23 | -0.07 | 0.08 |
| HUES6 | -0.78 | -0.26 | -0.51 | -0.05 | -0.47 |
| HUES8 | -0.15 | 0.69 | -0.17 | 0.68 | 1.45 |
| HUES9 | -0.89 | 0.31 | -0.75 | 0.51 | 0.37 |
| HUES28 | -1.33 | -0.11 | -0.91 | 1.03 | -0.07 |
| HUES44 | 0.70 | -0.27 | 0.52 | -0.48 | -0.45 |
| HUES45 | -0.46 | -0.26 | -0.49 | -0.02 | 0.65 |
| HUES48 | 0.83 | 0.18 | 0.70 | 0.24 | 0.55 |
| HUES49 | 0.19 | 0.07 | 0.03 | -0.66 | -0.26 |
| HUES53 | -0.95 | 0.65 | -1.19 | -0.22 | -0.20 |
| HUES62 | 0.25 | -0.15 | 0.15 | -0.60 | 0.24 |
| HUES63 | 0.62 | 0.39 | 0.72 | 0.34 | 0.61 |
| HUES64 | 1.45 | -0.07 | 1.44 | -0.56 | -0.61 |
| HUES65 | 0.19 | 0.02 | 0.22 | 0.19 | -0.15 |
| HUES66 | 0.59 | -0.67 | 0.36 | -1.22 | -0.37 |
| H1 | 1.54 | -0.29 | 1.21 | 0.07 | -0.56 |
| H9 | 1.08 | 0.01 | 1.10 | 0.55 | -0.16 |

Differentiation propensity: high medium low

| Cell line | Neural lineage | Hematopo-ietic lineage | Ectoderm germ layer | Mesoderm germ layer | Endoderm germ layer |
|---|---|---|---|---|---|
| hiPS 11a | -0.69 | 0.18 | -0.37 | -0.23 | 0.83 |
| hiPS 11b | -1.17 | -0.23 | -0.96 | -1.03 | 0.47 |
| hiPS 11c | -0.22 | 0.40 | -0.03 | -0.16 | 0.37 |
| hiPS 15b | -0.48 | -0.78 | -0.63 | -1.11 | -2.49 |
| hiPS 17a | 0.19 | 0.05 | 0.33 | 0.00 | 1.16 |
| hiPS 17b | -0.07 | -0.48 | -0.02 | -0.83 | 0.20 |
| hiPS 18a | 0.28 | -0.52 | 0.31 | -0.67 | 0.20 |
| hiPS 18b | 0.80 | -0.72 | 0.84 | -0.62 | 0.15 |
| hiPS 18c | 0.93 | -0.65 | 1.05 | -0.41 | 0.10 |
| hiPS 20b | -0.37 | -0.47 | -0.30 | -1.16 | 0.56 |
| hiPS 27b | 0.52 | -0.50 | 0.68 | -0.71 | -0.42 |
| hiPS 27e | -1.61 | -1.04 | -2.12 | -1.82 | -3.27 |
| hiPS 29d | -0.25 | -0.04 | 0.00 | -0.11 | 0.83 |
| hiPS 29e | -0.99 | -0.60 | -1.15 | -1.14 | -1.08 |

Differentiation propensity: high medium low

**Figure 6: Scorecard. Quantitative differentiation assay measuring cell-line-specific differentiation propensity**

## 2.2 Constructing iPSCs as Translational Devices.

The above described procedures constitute the "core" of the iPSC research platform, around which a number of interlocking features conjured up to trigger and solidify visions of soon-to-be reaped clinical opportunities for iPSCs.

Bypassing embryos as a source of pluripotent stem cells, laboratory and clinical research with iPSCs - albeit not devoid of ethical quandaries of their own (Testa 2009; Zarzeczny et al. 2009; Blasimme and Dröcher 2011; Cattaneo et al. 2013) – have been

framed and constructed, from the very beginning (Takahashi and Yamanaka 2006; Yu et al. 2007; Takahashi et al. 2007), as a more viable and less regulation-hindered alternative (Hauskeller and Weber 2011) to the ethically-contested and politically-charged research involving human embryonic stem cells (hESC). For instance, Takahashi and Yamanaka's seminal 2007 paper explicitly refers to "ethical difficulties regarding the use of human embryos" as an incentivizing factor for the envisioned generation of pluripotent cells directly from the patients' own somatic cells.

At the same time, iPSC-based technologies have consistently navigated a more accessible and academy-driven patent landscape (Roberts et al. 2014, field notes 2015) compared to that of hESCs, that has been largely dominated by both moral objections and legal restrictions to the allocation of property rights on embryo-derived cell lines, as well as the monopolistic scope of the Wisconsin Research Alumni Foundation (WARF) patents (Bahadur and Morrison 2010). As a representative from a company involved in iPSC research observed:

> *The patent situation for hESCs was much more complicated vis-à-vis iPSCs, when it is much clearer that, to work with iPSCs, you need to get a license from Japan. Moreover, in the EU you can't patent hESCs, and in the US those who held the patents were really strict, whereas in Japan they are much more research friendly, and willing to let you go along with your research.*
>
> Interview with representative of company involved in iPSC research

Taken together, these distinct tenets have greatly streamlined a vast amount of cognitive, material and financial resources - by public agencies as well as re-incentivized private investors alike - towards the rapid development of iPSC-based technologies.

Moreover, the relative ease of procurement of the primary material (typically skin or blood cells), and of transcription factor-induced reprogramming *per se*, provided a major facilitation vis-à-vis the socio-technically laborious (Waldby and Mitchell 2005), low-

yielding - and as of 2013 yet elusive, with regard to karyotype normality (Tachibana et al. 2013) - process of deriving human pluripotent stem cells by means of somatic sell nuclear transfer (SCNT). Whereas in fact therapeutic cloning can be seen as a technically "dirty and time–consuming process" (Germain 2013), also requiring the *disentanglement* (Callon 1998) of a socially and ethically valuable entity, such as an oocyte or an embryo, "from the networks of embodied social relations in which [it] originate[s]", in order to position it as "a technical entity whose productivity is at the disposal of the laboratory" (Waldby and Mitchell 2005), iPSCs require a much more straightforward procedure. Insofar as skin samples can not only be easily procured and reprogrammed into stem cells, but are also commonly associated with a category of *waste*, i.e. as something possessing no value or interest for the person from whom it originates (Waldby and Mitchell 2005)[3], they are much more easily mobilized in research practice, thus allowing the streamlined derivation of a vast number of pluripotent stem cell lines.

This very ease was in turn pivotal for the main aspect that sets iPSCs apart from their embryonically-derived counterparts in terms of translational potential, namely their patient- and disease-specificity. Precisely insofar as they could be easily derived from patients, and provide experimental accessibility to previously inaccessible cell types (such as neurons), iPSCs allow the generation of more faithful, less-mediated models of human disease compared to hESCs or animal models[4]. As such, they are seen as "invaluable tools for understanding disease mechanisms", a feature that in turn is geared to provide "new opportunities to develop medical therapies" (Nobel Assembly 2012).

[3] Not only defined in terms of its value (the "zero degree of value"), "waste", note Waldby and Mitchell drawing from cultural critic Walter Moser, implies a certain relationship between fragment and totality. As Moser (2002, quoted in Waldby and Mitchell 2005) writes: "Waste is often fragmentary, partial, residual in relation to a totality that would have pre–existed it. The French *déchet* – singular, nominative – conveys this sense better perhaps. The separation of the part from whole is usually one of the genetic pre–conditions for the existence of waste… waste is that part which has been actively detached (torn, ejected, expelled) from a whole and subsequently cast off and excluded: refuse"

[4] For an in-depth epistemological discussion on iPSC-based modeling, something that is beyond the aim of this thesis, see Germain (2013).

### 2.2.1 iPSC–based disease modeling: translating diseases in space and time.

As noted by Merkle and Eggan (2013), *in vitro* disease modeling with hPSCs has significantly benefited from the confluence of three technologies: the torrent of genomic data associating genetic variants to disease phenotypes, the ability to generate patient-specific iPSCs and differentiate them into cell types affected in disease, and powerful new tools for the manipulation of the human genome (allowing what Adamo, Atashpaz, Germain et al. (2015) define the "functional annotation of human genomes").

Through this technological convergence, iPSC–based models provide a *molecular translation* of disease within an *in vitro* system through the (not so trivial, see Germain 2013) task of identifying, by means of comparison (i.e. looking for differences) between control- and patient-derived cells, an *in vitro* phenotype that "recapitulates" (Grskovic et al. 2011) the clinical condition of experimental interest.

In their research practice, scientists have thus increasingly employed iPSC–based models in order to create *spaces of representation*, i.e. models established for "engendering things that otherwise cannot be grasped as objects of epistemic action" (Rheinberger 1997), that allow to align genetic lesions to data obtained from the clinical history of the patient, or, as some proponents of the technology belonging to my group have stated, to "bridge" the patients' genotype to clinical phenotype in developmentally relevant human cell lineages (Cattaneo et al. 2013; Adamo, Atashpaz, Germain et al. 2015). This "bridging" – which could be easily characterized in terms borrowed from semiotics as the establishment of a *signifying relationship* in which the genotype of the patient *stands for* its clinical phenotype, and viceversa[5] – opens up a twofold important experimental possibility.

[5] In particolar, drawing from Peircean semiotics, we could define the "bridging" occurring through the establishment of the *in vitro* phenotype as the establishment of a signifying relationship of indexical nature.

In the first place, described as experimentally fungible diseased "*avatars*" (see, e.g. Solomon 2012), iPSCs promise to make the impact of individual genetic variation on health and disease experimentally tractable (Adamo, Atashpaz, Germain et al. 2015). Put otherwise, in their guise of cellular models genetically matched to the patient - a feature which have prompted some practitioners to refer to them as to "the new patient" (Bellin et al. 2012; see also Goldstein 2012), thus assuming a reductionist stance which problematically gets rid of the normativity inherent to the lived experience of disease (Canguilhem 1978; Saha and Hurlbut 2011) – iPSC–based models enable to probe experimentally, for the first time in the history of medicine, the molecular contribution to disease in different genetic backgrounds, in a way conducive to the obtainment of more robust results across the broader patient population and the pursuit of promising lines of enquiry within the framework of personalized medicine[6].

In the second place, other than translating disease *in space*, by recreating *in vitro* the affected cell or tissue type(s), as well as reproducing the cell–context interaction (Mariani et al. 2012, Lancaster et al. 2013), iPSCs can be said to *translate disease in time*, by providing a *developmental replay* of its symptomatic as well as pre-symptomatic phases.

Indeed, the transition from a pluripotent to differentiated state is not only meant to provide differentiated cell lines to be probed experimentally for the disease of interest, but can also be, in itself, the focus of research (Germain 2013). For, *in vitro* differentiation is intended to replicate, or “mimic”, *in vivo* development and hence to “recapitulate” disease onset and progression. Thus, iPSC–based models allow to track the 'history' of disease as it affects *early* developmental lineages (and even the pluripotent stage itself, see e.g. Adamo, Atashpaz, Germain et al. 2015) which can be of potentially high informative value about

[6] This feature has prompted a possibly far-fetched visions pointing to a future in which "it will become routine not only to access the complete genetic information of a patient but to directly probe the patient’s own iPSC-derived tissues for a broad range of medical questions.” (Lee and Studer 2010).

the disease-relevant pathways affected by genetic mutations; in turn, they can be valuable to provide insights into the pathophysiology of disease and the discovery of new prognostic biomarkers whereby, for many diseases, “subclinical developments” (i.e. the pre–symptomatic phase of disease) may occur earlier than disease onset, while maintaining a causative relationship with the latter (Colman and Dreesen 2009).

Thus, as one scientist has put it, iPSC disease modeling (what some proponents of the technology have called the 'disease-in-a-dish' approach (Unternaehrer and Daley 2011)) is a key tool for "drilling down" to fundamental disease mechanisms that are neither immediately evident nor accessible to study in the clinical presentation of the disease (iPSC scientist, quoted in Saha and Hurlbut 2011).

Experimentally, in virtue of the genotype-phenotype alignment, iPSCs offer a bidirectional and iterative road between clinical care and experimentation - a feature that, as we observed in the previous chapter, is seen by advocates of translational research as one of its enabling asset to repair the lag in the clinical application of biological discoveries.

As extensively described by Germain (2013) in his study of iPSC–based modeling, the clinical phenotype serves as the basis for the discovery of the *in vitro* phenotype of the disease, whose 'rescue' by means of either gene editing technologies or a tested compound, can, in turn, generate findings to predict clinical outcomes in patients (Grskovic et al 2011). In more applied lines of research (see below), such as drug discovery, this bi-directionality manifests itself in the fact that “iPS cells can be generated from any human who is taking a medicine. Thus, any effect or lack of effect of a particular drug that is detected during clinical treatment can be re-analysed using iPS cells from patients.” (Nishikawa et al. 2008).

For all of the above, iPSCs offer a crucial translational advantage with regard to hESCs models. Whilst - other than limitations owing to its yield, and leaving aside the regulatory hindrances that have surrounded the hESC technology in many countries worldwide - it is in principle possible to obtain disease-specific pluripotent cells from embryos, either through genetic modification of existing hESCs, or the generation of new hESCs from embryos carrying simple, monogenic diseases detectable via preimplantation genetic diagnosis (PGD), some insuperable epistemic hurdles persist with regard to hESC disease modeling.

Notably, insofar as defected embryos are typically discarded, one cannot observe how the given genetic lesions affect the patient's clinical phenotype in the course of its lifespan, thus depriving pluripotent stem cell modeling of its very richness (i.e., the bi–directionality from clinical observation to molecular characterization, and back), and thus significantly hampering its heuristic power[7].

As a leading Harvard stem cell scientist - who took part from very early on in the process of hESCs derivation, and is now spearheading research with iPSCs - summed up the major experimental advance represented by iPSCs with respect to hESCs:

> *You use iPSCs because you want to understand the disease, and iPSCs are associated with the person, who has a lot of clinical information. hESCs never had that, it is not related to the disease, and you don't have those information. You may have some inborn genetic variations or errors, but you never know what the consequences of the variations might have been in the development of the organism. So, once you have made 30, 40, or 50 hESC lines, you don't have a need to make any more. I even asked that question myself [...]. We made 64 hESC lines, and I'll be honest, out of these, my lab used only between 4 and 6.*
>
> (Interview with Harvard stem cell scientist)

[7] As noted by Colman and Dreesen (2009) to explain this point: "Many genetic diseases display variable penetrance and severity of clinical symptoms from patient to patient. This lack of consistency is due to the complex interactions of genetic background and environment and may extend to the properties of derived pluripotent stem cells."

## 2.3. Constructing narratives and expectations around iPSCs' therapeutic potential.

In light of these features, reprogramming technologies have been widely adopted by laboratories worldwide, and have played an enabling role in spawning new avenues of clinical and pharmaceutical research. On one side, iPSC-based technologies have raised prospects for drug discovery. On the other side, albeit most likely in a longer timeframe and through a more tortuous translational trajectory, iPSCs-derived cells are predicted to become powerful translational objects themselves in the treatment of degenerative diseases, through the autologous replacement of affected cell types (Bellin et al. 2012; Cyranowski 2014).

Interesting to point out, in this regard, is how the 'mobilization of hope' (Kitzinger and Williams 2005), that constitutes an important component of the translational narrative revolving around iPSCs, shifted from an initial focus on the employment of iPSCs in regenerative applications to their usage in the drug discovery process.

Since Yamanaka's discovery in 2006, the "naïve expectations" (interview with UK stem cell scientist) that mobilized the imagination of scientific and policy communities, thus helping to gather and consolidate interest and resources in the field, as well as to provide legitimacy to it, were that iPSCs would have provided a catalysis for cell therapy[8], and hence enable a quantum leap in the realization of the promethean – and as yet mostly elusive – promise of an entire field of research (Hauskeller and Weber 2011; Thompson 2013; field notes 2015).

[8] Not only were indeed iPSCs to bypass the need for human embryos, but also greatly reduce the risk of immune rejection derived from the usage of hESC lines not matched genetically to the patient.

In the introduction of their landmark 2006 paper reporting the reprogramming of mouse fibroblasts, Takahashi and Yamanaka already presented the envisioned usage of iPSCs for cell therapy as one – and possibly *the* – main motivation for their work (Takahashi and Yamanaka 2006; see also Germain 2013). As they introduce the new technology, they explicitly frame iPSCs as a technical and ethical advancement vis–à–vis hESC–based regenerative therapies:

> *Human ES cells might be used to treat a host of diseases, such as Parkinson's disease, spinal cord injury, and diabetes (Thomson et al., 1998). However, there are ethical difficulties regarding the use of human embryos, as well as the problem of tissue rejection following transplantation in patients. One way to circumvent these issues is the generation of pluripotent cells directly from the patients' own cells.*

Similarly, in the first paper providing proof–of–principle of the therapeutic potential of iPSCs, published in *Science* in 2007 by Rudi Jaenisch's group at the Whitehead Institute (MIT), Jacob Hanna and colleagues argued that "the ethical debate over 'therapeutic cloning,' as well as the technical difficulty and inefficiency of the process, has spurred the quest to achieve reprogramming of somatic cells by defined factors" (Hanna et al. 2007). And as Yamanaka himself, in a 2007 paper on *Cell Stem Cell*, reviewed the different techniques for deriving patient–specific pluripotent stem cells, he explicitly positioned reprogramming technologies as means to achieve, through the generation of pluripotent stem cells directly from cells obtained from patients, one the "ultimate goals in regenerative medicine".

However, even though the promethean ideal of replacing damaged body parts constituted an enticing reservoir off which to feed the translational imaginary for the iPSC research community, resources in the field – with some notable exceptions – were for the most part funneled in a different direction, namely towards the establishment of robust

protocols of iPSC–based models of diseases, that served then as the basis for the development of assays for drug discovery.

Many scientists and investors were in fact quick to realize a simple thing. Namely that clinical translation of iPSCs – whose narrative, as I have expounded in the previous chapter, hinges on a rhetoric of acceleration that dictates the rapid achievement of tangible outcomes – would have been more easily pursued through the streamlined path of drug discovery, rather than the lengthier and more rugged route of regenerative therapies. Observed a US stem cell scientist:

> *The impact from modeling and drug testing will be in a much shorter timeframe than therapeutics (cell therapy). The process is challenging, managing risk, getting the right cells, having the cells go to the right place... And there's also another limiting factor: if you don't know how to do something, you don't know if you are 1 year or 10 years away. That's why people have mostly taken the quicker road of modeling and drug testing…*
>
> (Interview with US stem cell scientist)

Moreover, cell therapy has been perceived as a financially riskier endeavor, for it requires a higher level of investment for an uncertain return, with companies adopting a rather cautious approach to pour resources in the area (McKernan et al. 2010; Webster 2013).

The standardization of the field, a necessary prerequisite to ensure the mobility of cell–based therapeutics across different institutional and jurisdictional places (Webster 2013), and thus their commercialization, presents indeed several layers of complexity. First, it requires the establishment of an as yet largely non–existent experimental infrastructure (consisting of GMP facilities, *in vivo* cell tracking technologies, 'clinical grade' culture media, etc.); second, the identification and dissemination of defined standards to reduce variability across labs (such as the definition of Standard Operating Procedures, and

'defined media' to help the reproducibility of cell batches); third, the standardization of the *material nature* of the cells themselves (Webster 2013), to turn them into easily marketizable commodities. In addition, other than these technical issues, the consolidation of the regenerative medicine field for iPSCs requires the establishment of a "non existent" "commercialization space" (GEN 2014)[9]. As the director of an iPSC laboratory in a Harvard–affiliated institution in Boston argued:

> *[iPSC–based cell therapy] is high risk, and it is very expensive, we are talking in most cases about individualized medicine, it is not an off–the–shelf product, it's not going to be a huge money–maker, it will take a lot of time for development. It is more comparable to a surgery than to a blockbuster drug, right? So, […] it is very risky for companies to pursue this, and the few that do obviously focus on off–the–shelf–like products, like oligodendrocytes cells, the Geron trials, pancreatic beta cells […].*
>
> (Interview with director of stem cell lab, Harvard–affiliated institution, Boston)

At the same time, advancing a new field of research involves the managing of expectations, which actively contribute to its consolidation (Brown, Rappert and Webster 2000). Sociologists of expectations have long since highlighted the performative role played by the latter in stabilizing new fields of research. As, for instance, Jenny Kitzinger (2008) notes: "expectations are performative, they help to set priorities and attract investment, and hence stabilize future scripts and increase the likelihood of a particular future being bought into being". At the same time, however, mismanagement of

[9] As attested by a GEN market analysis of the "iPSC commercialization space", as of 2014 the market for iPSC research has mainly consisted in the commercialization of technologies for the "life sciences research space", and an "expanding" market segment in the utilization of iPSCs and iPSC–derived cells in drug development activities, whereas the third market segment of iPSC for cell therapies is deemed as "non existent at the moment".
Furthermore, the stabilization of the regenerative medicine field for has required the mobilization of *ontological politics* (Mol 1999) and the co–construction (Faulkner 2012) of an *ad hoc* regulatory landscape for their accelerated clinical deployment, as attested by the creation of Advanced Therapy and Medicinal Products (ATMP) regulation in the EU, and the Amendment to the Drugs and Medical Devices Law in Japan. In the paradigmatic case of the ATMP regulation in the EU, for instance, ontological politics was required to tame the unruliness of these novel biomedical entities and fitting them into a well determined ontological and regulatory category in order to accelerate their clinical deployment.

expectations can also generate setbacks, thus hampering the effective consolidation of the field. As remarked by the aforementioned director of an iPSC laboratory in a Harvard–affiliated institution in Boston:

> *Also, I think there are expectations... Because there has been a lot of hype around stem cells... You want to find the balance, you don't want to feed into that hype, you don't want to jump ahead too much, but you also want to avoid what happened with gene therapy, there was first hype, then setbacks, and now in the view of the general public, when the field is maturing and there are good procedures, is not a big thing... It can be a death sentence if something takes too long, and funds dry out. Or, if you are moving ahead too fast, you can have bad outcomes...and just a bad outcome in the news can be a death sentence for a company and the field for the funding situation.*
>
> Interview with director of stem cell lab, Harvard–affiliated institution, Boston

## 2.4. Translating iPSCs in Drug Discovery.

For all these reasons, with the most notable exception of Japan[10], which has devoted a substantial amount of resources to develop platforms for iPSC cell therapy in order to affirm its primacy in the field, the translational component of the stem cell field has revolved around the development of assays for drug discovery

Through increased efforts at maximizing yield and standardization (Unternaehrer and Daley 2011, McKernan and Watt 2013), iPSC-based technologies have been incrementally deployed as *translational tools* in the drug discovery process, where they are deemed to play a significant role in the conjoined efforts of public and private actors at halting the

[10] Exploring regenerative medicine and stem cell policy in Japan, Mikami (2014) introduces the idea that sociotechnical imaginaries can cause a lock-in effect on national science policy. In the context of Japan and stem cells, imaginary lock-in means there is an undesirable level of inflexibility, resulting from the state's early commitment informed by its vision of the nation's future. The situation of lock-in in Japanese science policy has, according to Mikami, emerged alongside governmental agencies' explicit announcements that the country aims to win the international competition in stem cell science.

purported productivity crisis in pharmaceutical RandD (Booth and Zemmel 2004; Paul *et al.* 2010; Pammolli *et al.* 2011; Light and Warburton 2011).

More to the point, by allowing testing for drug efficacy and toxicity in a disease- and patient-relevant context (Engle and Puppala 2013; Tang et al. 2015), iPSCs are geared to a twofold advance in the quest for innovative therapeutic compounds.

In the first place, they promise to effectively address what has been portrayed as a significant contributing factor in the high attrition rate in the development of first–in–class drugs, namely the molecular reductionism inherent to the target-based approach to drug discovery (Sams-Dodd 2005; Nolan 2007; Swinney and Anthony 2011; Scannel et al. 2012; Swinney 2013). Contextually, they are geared to open up new possibilities for drug screening programs based on phenotypic assays (Engle and Puppala 2013; Tang et al. 2015).

Starting to be widely adopted within the pharmaceutical industry since the dawn of the genomic era in the 1990s, following the commercial success of the cancer drug imatinib (Gleevec) (Keating and Cambrosio 2011), target-based drug discovery requires the formulation of a specific molecular hypothesis concerning the drug-target interaction, which is then tested, usually with biochemical assays, by measuring the effect of the compound against a single, well-defined target (such as a purified protein). On the contrary, the phenotypic-based approach requires minimal prior assumptions regarding a tested compound's molecular mechanism of action, and can also better address the complexity found *in vivo* by measuring the induced effects of new compounds in cells, tissues or whole organisms (rather than in 'idealized' setting such as a purified target protein), and then observing their phenotypic alterations.

In recent years, on the backdrop of the purported lack of *efficiency* (Paul et al. 2010) of the (predominant) target-based strategy for the discovery of first-in-class drugs (Swinney and Anthony 2011), owing to the little relationship occurring between *in vitro* assays and *in vivo* clinical responses, and the difficulties in rationally identifying, from all of the

potential molecular interactions, the specific ones that will contribute to an optimal pharmacological design (see, e.g. Nolan 2007), emphasis has been increasingly shifting towards a different approach to drug discovery, geared to include phenotypic-based assays in a more prominent way (Nolan 2007; Swinney and Anthony 2011). As Nolan (2007) has wryly noted to underscore the urgency of this shift in paradigm: “We don’t make drugs to save the lives of cell lines or to better the existence of bacterial extracts filled with overexpressed kinases!”.

In this scenario, the use of iPSC-derived cells in phenotypic-based assays is predicted to substantially improve their effectiveness, and thus increasing the likelihood of successfully translating preclinical discoveries to the clinic (Engle and Puppala 2013). In particular, while providing a physiologically relevant context in which to carry out drug testing, iPSC-derived cells are seen as effectively addressing some issues inherent to the so far standard use of directly isolated primary cells in these kinds of assays. Not only, as noted above, can iPSCs provide access to previously inaccessible cell types, such as neurons. In parallel with unlimited proliferation capacity, they also maintain a more stable phenotype in long-term culture vis-à-vis primary cells, thus being scalable and amenable to automation; and they allow to test multiple cell types from the same patient, so as to measure compound toxicity in different cellular settings (Engle and Puppala 2013).

Morevoer, patient- and disease-specific cells are predicted to conduct the so-called 'in vitro clinical trials', in which iPSCs derived from a wide variety of individuals could be used to predict patients’ response to a drug, while also allowing for direct testing of potential new drugs in samples from target populations, thus directly supporting initiatives in precision medicine (Engle and Puppala 2013). As attested by a prominent Harvard stem cell scientist:

> *That's the idea, that you are going to use the exact same cells to make cardiomyocites, liver cells - the two most reasonable cells in terms of toxicity -, and see how they are affected. People have talked about it a lot, none has done it yet. Kevin*

*[Eggan] is on the path of doing it, and this could revolutionize the way we think about clinical trials and drug development.*

Interview with Harvard stem cell scientist

## 2.5. Conclusions.

This chapter has served the purpose of providing an eagle eye view of the iPSC research landscape. From the standardization of research practices, to the constructions of narratives and expectations around the therapeutic potential of iPSCs, to their deployment in pharmaceutical research practice, I have here accounted for the multiple, intertwined ways in which iPSCs have been constructed as prominent translational devices.

Invested with high hopes and expectations within what Charis Thompson (2013) has aptly defined a *pro–cures–as–innovation* framework, in which its translational potential is intimately tied to a rhetoric of innovation, iPSC research has progressively positioned itself as a mainstay of advanced as well as developing stem cell-based bioeconomies and knowledge-based societies worldwide. Governmental agencies and private investors, in Western and Asian countries alike, have mobilized a large amount of material, financial and cognitive resources geared to the establishment of state-of-the-art biomedical platforms (Keating and Cambrosio 2003), as well as bio-networks (Patra and Sleeboom-Faulkner 2009; Sleeboom-Faulkner and Patra 2011) operating on iPSC at the transnational scale (e.g. Mikami 2014; Sleeboom-Faulkner and Hwang 2012; Thompson 2010, 2013; Zhang 2011). While the Japanese case stands out owing to sustained state-led efforts at primacy in the field (Mikami 2014), iPSC research platforms worldwide both collaborate and compete in standardization practices aimed at stabilizing the field (Webster and Eriksson 2008; Webster 2013). In parallel, they strive to develop models of governance that could successfully advance desired framings of iPSC-based innovation, so as to gain competitive advantage in the distinct yet interlinking markets of scientific credibility,

intellectual property rights, biomedical commodities and socio-political prestige (Salter 2013).

Against this backdrop, an important point should be clarified in conclusion. The topography of the field of somatic cell reprogramming that I provide in this chapter may run the risk – given the inevitable generalizations warranted by such a rapid overview – of projecting an *essentialized* image of iPSCs research, as a well–defined landscape defined by immovable signposts, in which the standardization and innovation paths follow a linear and uniform trajectory.

On the contrary, I would like to argue, the stabilization of the iPSC research field does not follow a linear trajectory, but develops along different, heterogeneous and sometimes competing pathways that involve a broad array of actors and practices (cf. Webster 2013). Thus, novel biomedical entities like iPSCs should not be understood as fixed substances defined by immutable properties, but rather as "informed material", as "entities whose shifting ontology depends on relations that can or cannot be established with other substances and practices" (Cambrosio et al. 2009). Put otherwise, the *pluri–potency* of iPSCs is not only brought to bear onto their material differentiation into different lineages, but also onto their openness to a multiplicity of standardization pathways and socio–technical futures. As the empirical chapters of this dissertation will show, depending on the different 'social matrix' in which they are made to attach, as they circulate across different platforms in distinct socio–political contexts, iPSCs are enrolled in distinctive innovation journeys (Van de Ven et al. 1999), where, at stake, is the co–construction of the material and the social (Webster 2007).

How these co–productive processes take place in American and European platforms is what I aim to expound, after a necessary methodological *detour*, in the following chapters of this dissertation.

# Chapter 3. Theories and Methods.

As I observed in the concluding remarks of the previous chapter, and as decades of STS and social sciences scholarship have long since shown, innovation in science and technology has a strong normative component embedded into it. Far from being the mere realization of affordances stemming from techno-scientific breakthroughs, as the so called, much-hyped, and widely criticized (see e.g. Godin 2006; Felt and Wynne 2007) linear model portrays it (Bush 1945; Nelson 1959), innovation is as much a statement about epistemic and technical ingenuity as it is an assertion of the norms, interests and values that enable it and underpin its circulation.

The interwoven nature of the normative and the technical within the fabric of innovation has been brought to the fore through distinct, but in fact convergent, analytic paths. On the one hand, work in STS has done much to illuminate the role played by normative commitments and complex socio-cultural dynamics in shaping the products of techno-scientific systems. On the other hand, an equally significant body of STS scholarship has coalesced around a broad understanding of innovation, which is framed as encompassing not only its technological yield, but also the societal (re)configurations required to both foster and accommodate the presence and circulation of novel material artifacts and technologies, in a process of reciprocal adaptation entailing the mutual constitution of techno–scientific and normative orders (Jasanoff 2004).

In line with the overall aim of this project to provide a yet unattempted cartography of iPSC-based innovation, and drawing from the latter strand of STS scholarship, which mostly owes, for its systematization, to the scholarship of Harvard professor Sheila Jasanoff and her work on the notion of co–production (Jasanoff 2004), in this chapter I aim

to lay bare, and critically dissect, the methodological toolkit that I will then deploy, in chapters 4, 5, and 6, in order to wade through my empirical case studies.

Consistent with the etymological polysemy of the word 'methods' (from the ancient Greek *metá–hodós*) – that bears reference to both the spatial dimension (the *'where'*) of a journey and the modality (the *'how'*) through which to undertake it – in the subsequent sections I will proceed as follows.

First, I review the salient features of the notion of *biomedical platforms*, as articulated by Peter Keating and Alberto Cambrosio, thus accounting for my choice of identifying leading iPSC research organizations as privileged sites for empirical analysis of iPSC–based innovation. A fundamental assumption underpinning this dissertation is indeed that, as argued in the introduction, it is the *meso*–scale of leading research platforms that represents the perfect analytic viewpoint for tracing the innovation trajectory of iPSCs (differently from the case of hESC research, which greatly owes for its innovation dynamics to the *macro*–scale represented by different national styles of regulation and civic epistemologies (Jasanoff 2005)).

Next, I refine and expound my analytic approach, geared to deploy the notion of *biomedical platforms* within Sheila Jasanoff's co-productionist framework (Jasanoff 2004) to build up the analysis of my empirical case studies. As I do so, and drawing from other theoretical approaches, I highlight what – at least for the purposes of this dissertation – are some of the analytic pitfalls of the scholarship revolving around the notion of platforms, namely its neglect of the ways in which the broader socio–political context in which platforms are situated affects their innovation dynamics. To address this shortcoming, I trace the distinction between an *endogenous* and *exogenous* form of co–production, and contend that both kinds of co–productionist accounts are needed in order to capture the dynamics of innovation in contemporary biomedical research.

### 3.1 'Platforms' as widespread actors' category.

In their in-depth, sociologically-informed work spanning a good part of the last 15 years, Alberto Cambrosio and Peter Keating have advanced the notion of *biomedical platforms*, aimed at providing both a far-reaching theorization and a thorough empirical account of the dynamics of contemporary biomedical innovation (Keating and Cambrosio 2000, 2003; Cambrosio et al. 2009). Heuristically powerful, semantically flexible, as well as descriptively rich, the notion of *biomedical platforms* constitutes an important theoretical backbone upon which the present work is built, and thus no doubt deserves its fair share of analytic scrutiny.

For those immersed in the field of biomedicine, as either analysts or practitioners, the notion of 'platform' is not an unfamiliar one. From 'genomic platforms' arising in a broad array of research institutions all over the world, to 'stem cell platforms' established within major pharmaceutical companies, to platforms developing around technologies such as microarrays or mass spectrometry, to public initiatives such as the 'UK Regenerative Medicine Platform' - to recall but a few instantiations of the term - the landscape of the biosciences is dominated by the ubiquitous presence of such multifarious 'platforms'.

As Cambrosio and colleagues note accordingly, "while social scientists are still likely to wonder about the meaning of 'platforms', this term is now commonly used and understood by natural scientists and clinicians" (Cambrosio et al. 2009) – and at an ever increasing rate since the beginning of the new century. A search for its occurrence in the title of articles listed in PubMed shows indeed that while the term 'platform(s)' was found on average in 27 titles/year during the 1990s, this average rose to 574/year during the 15-years period 2000-2014, with a staggering 1133 results/year in the last 5 years (2010-2014).

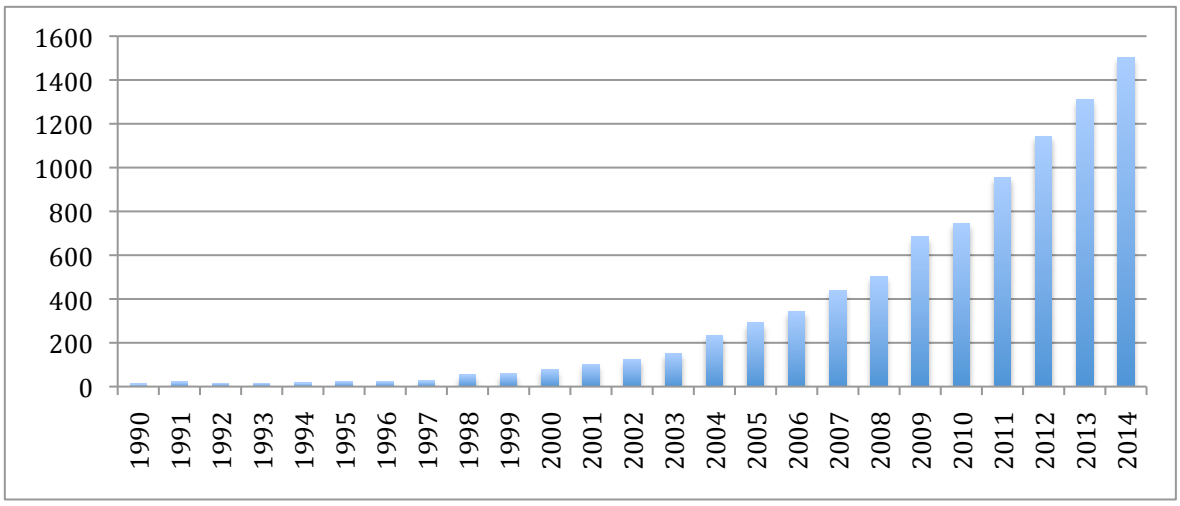



**Table 1. PubMed Research of the term(s) 'platform*' in 'titles'.**

Not just a mere resultant of the analyst's propensity to abstraction, the notion of platform is thus a widely circulating category, employed by actors themselves in reference to a broad range of practices, programs, technologies.

In particular, in its 'common sense'/'native' meaning (i.e., as an *actor category*), the notion of 'platform' revolves around three main usages. First, platforms refers to *sets of techniques and technologies* mobilized by research domains increasingly reliant on the use of complex instruments that often combine biological reagents and digital equipment, with the varied -omics technologies being a conspicuous case in point (Cambrosio et. al 2009). In a similar fashion, the term is also used as a synonym of, or in relation to, *core facilities*, namely, a combination of laboratory instrumentation and associated skills shared by researchers from one or more institutions, to streamline what are considered routine experimental practices, but which are generally too expensive, complex or specialized to be sustained by a single laboratory or small group of researchers themselves (Cambrosio et. al 2009; Ernst and Young 2012; see also chapter 5). Third, 'platform' often maintains an *institutional connotation*, whereby it replaces notions such as 'initiative', 'program' or 'network' in reference to publicly-supported and often interdisciplinary endeavors aimed at

tackling scientifically as well as socially relevant issues, by means of collaborations among a typically broad variety of actors (SAHN 2014).

## 3.2 The performative hybridity of biomedical platforms.

The semantic amplitude of the term, that bears reference to experimental and technological arrangements, as well as institutional configurations, is maintained, and in fact harnessed, by the analytic rendering proposed by Cambrosio and colleagues.

The notion of *biomedical platforms* set out to "draw together, within a single category, biomedical instruments and programs and related patterns of cooperation between biologists, clinicians, and companies that produce reagents and equipments" (Keating and Cambrosio 2003). Analytically, it thus serves the purpose of capturing, and making amenable to thorough empirical investigation, a defining feature of contemporary biomedical research, namely its increasing reliance on *hybrid* forms of *inter–disciplinary* and *inter–institutional* collectives[1].

The concept of *hybridity*, in particular, maintains a key saliency for Keating and Cambrosio's characterization of biomedical platforms.

At a first, and coarse-grained, level of analysis, a platform's hybridity can be characterized - in a way reminiscent of Latour's own definition of networks as amalgamations of social and natural constituents (Latour 2012) - as the establishment of *linkages* among a broad array of actors and technologies, operating within different

[1] More extensively, biomedical platforms can be defined as "stabilized interconnections between new biomedical entities (e.g., genes and mutations, existing as both material and representational entities), the sets of technologies (equipment, related reagents, etc.) necessary for their manipulation and representation, and the regulations (standards, nomenclature, quality norms) that are constitutive of their proper use in clinical and laboratory settings, and in particular at the laboratory-clinical interface" (Cambrosio et al 2009). According to other definitions provided by the authors, the notion of 'biomedical platforms' designates "Specific combinations of techniques, instruments, reagents, skills, constituent entities (morphologies, cell-surface markers, genes), spaces of representations, diagnostic, prognostic, and therapeutic indications, and related etiologic accounts." Furthermore, platforms are "material and discursive arrangements that act as the bench upon which conventions concerning the biological or the normal are connected with conventions regarding the medical or pathological."

disciplinary contexts while often belonging to distinct institutional backgrounds, spanning from the scientific to the industrial, from the governmental to the non-profit sector.

Indeed, at both the *micro*- and *meso*-level of individual labs and research organizations, the dominant epistemic culture (Knorr-Cetina 1999) in contemporary biomedicine builds on, and is shaped by, the alignment of a broad array of actors embodying a distributed form of cognition and scientific expertise (Giere 2002); the recourse to varied sets of complex instrumentations (Keating et al. 1999), requiring dedicated (and often tacit) skills for their functioning (Polanyi 1958; Knorr-Cetina 1999); the contribution, and close-hand involvement, of equipment and reagents providers, oftentimes performing an indispensable ancillary role in the set-up phase of experimental systems and standardization technologies.

Similarly, at its *macro*–level, the institutional configuration of biomedical research is increasingly reliant on the establishment of large, trans–institutional research consortia. Andrew Webster (2015) notes that

> *A significant characteristic of the science system today is the growth of large-scale 'platforms' that support and align national and international networks, and might be seen as the defining feature of contemporary 'research infrastructures'.*

Hence, while collaborative research is in itself nothing new, contemporary developments in the life sciences, especially since their post–genomic translational turn, reveal a "qualitative shift" in the way in which epistemic communities and their networks are configured (Webster 2015): from the ample diffusion of interdisciplinary and trans-institutional collaborations; to their '*projectification*' (Vermeulen 2015), through the institutionalization of practices of coordination among actors (Webster (2015) cites the advent of ubiquitous 'work-packages' and associated 'deliverables' as a prime example of management strategies meant to ensure "that research can be managed across diverse groups and interests [...], while each retains a specific, discrete responsibility and

intellectual home in which they feel comfortable"); to the increased relevance of practices of standardization, aimed at both establishing consensus between different laboratories (Cambrosio et al. 2006) and patrolling the boundaries and entrance gates of emerging fields of research (Webster and Eriksson 2008; Busch 2013).

In a first sense, the notion of platforms thus points to a marked increase in complexity in the configuration of biomedical research, on the backdrop of which, so the argument goes, it would be impossible to account for innovation in the field of biomedicine without referring to the *heterogeneous*, *multi-disciplinary* and *cooperative* nature of its current practices.

Secondly, at a more fine-grained level of analysis, the notion of hybridity refers to the development of new interactions, dependencies and arrangements resulting from the *blurring* of organizational and knowledge boundaries along public-private and laboratory-clinical gradients. Similarly to the rise of a 'hybrid culture' out of a new articulation - rather than the juxtaposition - of different practices of knowledge-making described by Strasser (2011), and the process of hybridization that bring together "things whose articulation, amalgamation or even blending was not assumed to lie in the nature of the things so brought together", theorized by Rheinberger (1997), the consolidation of platforms propels the *reconfiguration* of contemporary biomedical practices and the creation of *new hybrid collectives and modes of practice*. In other words, rather than interfacing well-defined, self-contained actors and organizations, each pursuing different aims according to distinct systems of incentives (Aggeri et al. 2007; Cambrosio et al. 2009), platforms promote the re-articulation of heterogeneous and distributed forms of expertise and the realignment of distinct (commercial, academic, non-profit) goals. Insofar as they enact a major form of coordination among actors, each bearer of its own disciplinary expertise, style of practice (Keating and Cambrosio 2011), as well as interests and aims, these hybrid formations bring about a profound reconfiguration of the institutional space underpinning biomedical

practice, in a twofold movement that, while it *feeds off* the actors' own actions to create a new field of practice, at the same time, and recursively, significantly *redefines* the actors' identity, agency, and goals (Latour 2005).

These two sets of converging features bring in turn to the fore a salient characteristic of platforms, namely their *performativity* in both defying, and reconfiguring, entrenched organizational and knowledge boundaries, and recasting the identities, actions and normative commitments of a broad variety of actors.

Through their *performing hybridity*, platforms both disrupt and stabilize, enabling the emergence of new organizational models, that in turn stabilize novel biomedical technologies, entities and practices with their attending epistemologies (Cambrosio et al. 2006; Keating et al. 1999) – all features of intuitive and immediate appeal for a technology such as iPSCs that is explicitly invested with the mission of forging a new alignment between biology and the clinic (see chapter 2).

Furthermore, and precisely through their hybrid performativity, biomedical platforms represent an important site of *value–articulation*, underpinning the making of "what comes to count as a relevant order of value in given situations, practices, socio-technical systems, institutions, and professional cultures"_(Dussauge et al. 2015). In other words, I take platforms not as mere *intermediaries* (Latour 2005) for the reproduction, or rehearsal (Felt 2015), of widely held commitments, expectations and imaginaries, but rather as *mediators* (Latour 2005) that re-articulate them in novel ways, with outcomes that can span the entire stabilization-disruption range, from the reinforcement of entrenched sociotechnical imaginaries (Jasanoff and Kim 2009, 2015) to their challenge through the projection of alternative framings and vanguard visions (Hilgartner 2015).

### 3.3 Accounting for the performativity of platforms: the *endogenous co–production* of scientific and governance innovation.

The hybrid performativity and flexibility at re-articulating, that characterize biomedical platforms, offer, in turn, the docking site for confronting the broader implications of iPSC research arrangements in terms of co-production (Jasanoff 2004).

In light of the above, a primary aim of the second part of this dissertation will be to investigate how, through the assemblage of a broad array of actors, technologies and practices, the three iPSC research platforms analyzed in this work perform, in their endeavors, the constitution of *epistemic* as well as *normative* orders, each underwriting the other's existence and consolidation.

In particular, consistent with the manifold articulations of the discourse and imaginary revolving around clinical translation (see chapter 1), I intend to analyze, *comparatively*[2], how the three iPSC research platforms re–articulate translation in a variety of different ways, producing distinct framings of the translational lag narrative, and materializing, through the enactment of specific modes of iPSC research practice, distinctive normative stances concerning social order and the collective good. Drawing from the approach recently proposed by Dussauge and colleagues (2015), I thus aim to craft an empirically sensitive account that, rather than treating the values and expectations underpinning translational iPSC research as something stable and predefined, as *given* entities endowed with explanatory powers, looks at how they are enacted, and co-produced (Jasanoff 2004), within and along with concrete epistemic practices[3].

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[2] The importance of comparison for the outcomes of the present work should not be underestimated. Comparison, notes Sheila Jasanoff (2005), is a powerful way to problematize the assumption of notions such as 'science', 'state', or 'society' as stable units of analysis, and "should be seen as a means of investigating the interactions between science and politics, with far reaching implications for governance in advanced industrial democracies".
In the case of three iPSC research platforms, thaty I analyze in this dissertation, they lend themselves well to comparative analysis by being different enough to present interesting contrasts, but similar enough for the variations to be disciplined (Jasanoff 2005). For this reason, they can be fruitfully employed as mutual "controls" in assessing their respective specificities.

[3] More to the point, write Dussauge and colleagues (2015), empirically sensitive accounts of this kind are particularly suitable to probe sets of questions concerning: (i) the co-production of the normative and the epistemic in scientific practice (how is knowledge produced, and produced *as valuable*?); (ii) the definition of matters of concern (which kind of knowledge is considered

More to the point, on the basis of the results presented in the empirical chapters of the dissertation, I identify two different ways of *applying the co-productionist lens to the analysis of biomedical platforms*, and I thereby propose a multi-scalar approach geared to analyze empirical evidence at different levels of interpretive relevance.

In the first place, building on Jasanoff's contention that "knowledge making is incorporated into practices of state–making, or of governance more broadly, and in reverse, practices of governance influence the making and use of knowledge" (Jasanoff 2004), I argue that biomedical platforms propel what I term the *endogenous co-production* (Marelli and Testa forthcoming) of *scientific innovation* and *regimes of governance*, through the adoption of mutually constitutive *standardization* and *governance* practices. For, as particular sociotechnical articulations of the translational visions are formed and tried into practice, they gain material currency in the establishment of specific practices and technologies of iPSC standardization, and the contextual implementation of distinctive regimes of governance (Hilgartner 2012, 2013).

Accordingly, the (endogenous) co–productionist account that I propose in this work is aimed at symmetrically probing: (i) how, by resorting to different strategies of standardization, that establish specific iPSC research technologies and infrastructures, and shape the material ontology of these emerging biomedical entities in distinctive ways, those iPSC research platforms pursue different paths to iPSC–based innovation; and (ii) how, by adopting specific regimes of governance that allocate agency and power among actors, define specific modes of accountability and steering mechanisms – thereby establishing a significant part of the constituency claiming jurisdiction in this domain of biomedicine – they uphold and give material instantiation to distinct socio–political expectations, interests and normative commitments.

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valuable and worth attaining? What comes to count as valuable, desirable, or otherwise worth caring for?) iii) the interrelations (alignments and tensions) among multiplicities of values (how are hierarchies among values established? How are boundaries and links made between notions of economic, epistemic, and cultural values?).

In proposing the notion of endogenous co–production, I draw on a number of studies that have investigated and brought to the fore the mutually constitutive relationship between scientific and governance innovation.

In particular, in his analysis of the establishment of the Human Genome Project (HGP), Stephen Hilgartner (2013) shows how, contextually to a substantial reconfiguration of the practices of genomic research, the HGP required, for its successful implementation, the creation of a new regime of governance establishing "control relationships" for allocating control among agents and specific "governing frames" that "provide an interpretive schema for identifying relevant agents, spaces, objects and actions, and promote an official view of how they are supposed to interact – for example, by defining rights and modes of accountability". In doing so, he crafts an ethnography–based account of the genome mapping and sequencing community in biomedicine that brings to the fore the "process of coproduction that constituted a new category of science – 'large-scale biology' – and the sociotechnical machinery for governing it" (Hilgartner 2013).

Adopting a political economy perspective, Brian Salter (2013) has instead more explicitly called attention to the innovative potential of the process of knowledge–production related to governance. The production process from scientific idea to marketable product, he argues, is long and tortuous, and requires more than just the scientific knowledge needed to conceive and develop products. What becomes crucial is also the production of new forms of governance knowledge that could help resolving the potential tensions of which the trajectory of innovation is rife with. Thus, governance becomes a site of innovation in its own right, and is to be co–produced with science. As he notes, "the production of governance knowledge takes place in parallel to the production of scientific knowledge: both are necessary if the progress of a concept from a scientific idea to marketable product is to occur" (Salter 2013).

Furthermore, in their study on the evolution of diagnostic and therapeutic practices in the field of medical oncology in the last 50 years, Alberto Cambrosio and colleagues (2014) have proposed the notion of *regimen* as an heuristic concept able to capture the mutually constitutive character of scientific knowledge and organizational and governance structures of clinical research (or, in other words, the co-production of oncology's epistemic content and institutional arrangements). As they write, this notion describes "the growing isomorphism between new objects in cancer research and the quest for organizational arrangements that could allow to change approach in a domain characterized by the increasing production of data produced by means of post–genomic technologies" (Cambrosio et al. 2014).

Tracing the development of clinical assays and protocols (whose staple came to be the distinction in "phases" (Phase I, II, III) within cancer clinical trials), they show how the new "stile of practice" (Keating and Cambrosio 2012) inaugurated by the assays represented, at the same time, as much an epistemic advance (insofar as it provided a renewed understanding of cancer and its potential therapies), as well as an innovation in the organization of cancer research (since it propelled the institutionalization of Cancer Cooperative Groups, that were then themselves responsible for the widespread introduction of the assays within clinical routine). What is more, they also show how, from the middle of the 1990s, the discovery of new targeted therapies (that act on specific molecular targets associated with cancer, rather than on whole subpopulations of cells) prompted not only a process of reconfiguration of clinical trials (introduction of Phase 0, 'hybridization' of Phase I and II, etc.) and the introduction of new kinds of assays (such as the neo-adjuvant approach, aimed at reducing the size of cancer, through chemotherapy, before surgical intervention), but also a profound reorganization of the governance structures of cancer research itself, which led to the demise of Cooperative Groups and the emergence of more flexible Cancer Consortia.

Drawing from all of the above, it is thus possible to elaborate a first set of questions that guide the analysis of the three case studies that I conduct in the empirical chapters of this dissertation. Hinging on the methodological approach that I have just proposed I will address these related sets of issues:

(i) Which norms and values are distinctively enacted and upheld by different platforms? How are the very notions of stem cell translational research and translational science policy being redefined, and differently performed, through such endeavors?

(ii) How, in the three different platforms under scrutiny, are different conceptions of what is valuable translational iPSC science being articulated, prompting the design of different iPSC-based research programs and technologies, alongside the implementation of distinct regimes of governance, modes of accountability, and steering structures?

(iii) Through which mechanisms, programs and practices do the governance and standardization practices being enacted on each platform come to sustain and reinforce each other?

### 3.4 Platforms–in–context. For a critical appraisal of Keating and Cambrosio's analytic framework.

These prior methodological observations represent an indispensible background to make sense of the structuring and functioning of the three iPSC platforms on which the present dissertation focuses.

At the same time, what ought to be recognized is how the *endogenous* dynamics underpinning the constitution of platforms, such as the ones I have so far accounted for in discussing the establishment of hybrid regimes of coordination among different actors, are not alone in shaping the organizational structure of the platforms, as well as their epistemic and normative performativity. The way in which platforms emerge and consolidate as specific socio-technical configurations, enact specific tropes of values and generate new

biomedical knowledge, is indeed something which is also heavily reliant - although not *stricto sensu* dependent, as posited by neo-institutionalist accounts (Powell and Di Maggio 1991; see also Bonazzi 2007) - on the *exogenous* conditions in which they find themselves to operate, or, in other words, on the relations that they establish with their outer socio-political context.

Put otherwise, *politics* writ large, other than *endogenous regulation,* plays a first-hand role in the assemblage of platforms, as it pre-structures the space that they are bound to inhabit (Powell and Di Maggio 1991), thus providing the epistemic, normative, and material resources and affordances that enable, as well as constrain, their developmental trajectory.

While not escaping the attention of Cambrosio and colleagues (see, for instance, Cambrosio et al. 2006; 2014), their scholarship remains in many ways unsatisfactorily muted towards this aspect. In a way reminiscent of a Derridean post-structuralist stance, and the contention that there is no external referent upon which any system of signification would be founded ("*il n'y a pas de hors-texte*", Derrida 2013), they maintain that no relation among actors exists independently of the very act of establishing it, and no such act is performed by an actor external to the platform, for "[a platform] has no outside" (Keating and Cambrosio 2003). Theorizing the self-contained dimension of platforms[4], their analytic framework set out accordingly to explore endogenous regulatory practices resulting in the definition of concerted programs of collective action and the establishment of consensus among actors within a given platform (producing what they term as a *regulatory* form of *objectivity*, see Cambrosio et al. 2006, 2009). In so doing, it lends itself to foreground processes of meaning- and value-making taking place *within* a given platform, while implicitly, if not programmatically, losing sight of the *exogenous* and

[4] Keating and Cambrosio (2003) assert that "while medical and lay actors position themselves vis-à-vis a given platform, contributing, for instance, […] to its further entrenchment, they cannot operate 'off' the platform".

*contextual* forms of coordination that equally contribute to a platform entrenchment and stabilization. Notably, their scholarship tends to dispense with a close engagement with the contingent norms and values, the broader political cultures and civic epistemologies (Jasanoff 2005), as well as the historically-situated market configurations or bioeconomies (Goven and Pavone 2014) that underpin, drive, and validate processes of knowledge-generation in the life sciences.

In reason of that, such *internalist* perspective[5] maintains what is, for the purposes of this work, a twofold shortcoming. In the first place, it omits from its topography the landscapes of power and normativity which represent, at the same time, the context of and the *conditio sine qua non* for the assemblage of biomedical platforms, thus remaining completely silent as to *why* these novel configurations are established in the first place. Second, while the 'platform' axiomatic (which maintains a family resemblance with that of the 'network', as conceptualized by ANT[6]) represents a potent analytic tool to account for how *ontological* orderings are enacted in relation to emerging techno-scientific practices, through the concerted efforts of a broad array of (human and non-human) actors, it seems less suited to address the *normative* and *political* questions of social macro-order to which major research programs in the life sciences inevitably lead[7]. Thence, while it makes possible to appreciate the socio-technical complexity that underpins the constitution of novel biomedical technologies, it has less to say on how these emerging configurations of techno-scientific knowledge are brought to bear on the configurations of political systems,

[5] For the purpose of the present discussion, I define as an *internalist* approach one foregrounding questions about the processes and negotiations through which knowledge is produced, whereas I define as an *externalist* approach one that takes scientific and technological practices as windows onto wider society and its ordering macro-structures of politics, law, and economics. Hence, I take a different approach from the one proposed by Steve Shapin (1992). For him, an internalist account of a particolar techno-scientific phenomenon focuses on the domain of theories and ideas, whereas an externalist account relates the emergence of certain teories or ideas to events that were going on in social and political culture at the time and place of discovery. As noted by Charis Thompson (2005) in expounding Shapin's perspective: "An externalist account of Newton's science would examine why he chose certain problems and certain resources in terms of the political context at the time. Materialist factors, such as the economy, rather than ideas, become the well- springs of change."

[6] For a critique of the ANT approach, see Jasanoff 2012 and Jasanoff and Kim 2015.

[7] For a compelling review of different approaches and strands of analysis in STS, see Thompson 2005.

thus not addressing the rather relevant issue of their socio-political implications. Against these deficiencies, a broader, contextualized view of the functioning of platforms, that takes into consideration its normative dimension as well, is thus required.

A fruitful approach geared to address these shortcomings is the one proposed by Sleboom-Faulkner and Patra (2009, 2011). Their work, much in Cambrosio and colleagues' vein, set out to explore the rapid expansion of collaborative endeavors in the life sciences, focusing in particular on the development of experimental stem cell therapies platforms in India and Japan. Differently from Cambrosio and colleagues' approach, however, their research program aims at generating a *contextualized understanding* of the rise of these stem cell platforms, as they reach beyond local spheres to facilitate interactions across national scales, and to this aim they elaborate the notion of *bionetworking*. According to their definition (Sleebom-Faulkner and Patra 2011):

> *Bionetworking is a social entrepreneurial network activity involving biomedical research and healthcare organizations that thrive under conditions of health inequality (Patra and Sleeboom-Faulkner, 2009). A bionetwork consists of a plurality of actors engaged in 'biotechnical ventures' (Waldby and Mitchell, 2007) working across geographical spaces, regulatory regimes and social institutions. A bionetwork exploits differences and similarities in the provision of healthcare, levels of wealth, standards of scientific development, and research regulatory regimes and their implementation.*

Differently from the notion of platform, that of bionetworking, rather than bracketing or explaining away the social and political context(s) in which platforms operate, zeros in on it so as to explain their functioning. In particular, *differences* and *asymmetries* in standards of scientific developments, regulatory conditions, healthcare access, political regimes and socio-cultural backgrounds are seen as powerful explanatory resources to make sense of

the configuration of collaborations on a transnational scale. A bionetwork, for instance, emerges out of connections created across two countries, such as India and Japan, in which discrepancies in healthcare coverage and regulatory standards allows for the provision of Japanese research grade stem cell technologies as therapeutic products within the Indian setting (Sleeboom-Faulkner and Patra 2011).

However, insofar as it focuses on discrepancies arising at a *transnational* scale, this approach can hardly be employed to account for differences in the configuration of platforms operating within the *same* political and regulatory context, or in different contexts characterized by *evenly balanced*, rather than lopsided, interdependencies. Furthermore, whilst conducive to account for the socio-political situatedeness of biomedical platforms, it seems less suited to address the symmetrical question of how emerging networks and collaborations, while feeding off a certain socio-political *milieu*, are also endowed with the capacity to reinforce (or challenge) their underpinning socio-political order. Indeed, insofar as this approach takes such underlying social asymmetries as an *explanans* for the configuration of emerging collaborative endeavors, it falls short in the scope of accounting for the *mutual* articulation (alignments and tensions) between research platforms and the broader societal landscape in which they are situated[8].

A thoroughly symmetrical approach accounting for both bottom-up (i.e., platform–driven) and top-down (i.e., context–dependent) dynamics in technological innovation is the one advanced within the so-called Strategic Niche Management research (henceforth: SNM). A key critical objective of this strand of scholarship is a technologically deterministic view of innovation, that – much in the vain of the aforementioned linear model – erects a clear-cut divide between object and context of innovation, and conceptualizes the creation and survival of technological novelty as a dynamic solely

[8] At the same time, this approach suggests a series of interesting research questions, such as: how are national boundaries transgressed and interconnections established in transnational collaborations? Which dynamics are in play in constituting biomedicine as a global enterprise? How do geopolitical asymmetries affect the emergence of new field of research?

inherent to intrinsic features of the former. In line with other strands of STS scholarship (see above), SNM scholars recognize instead that the stabilization of emerging technologies requires interrelated social and technological changes (Schot and Geels 2008). Sustainability of novel technologies, in other words, hinges on the alignment, or co-construction, of technology and society, that which leads to the establishment of *technological* and *innovation niches* (*ibid.*).

Particularly apt for the purpose of explaining the socio-economic entrenchment of radical technological novelties, such as *disruptive* types of technologies (Christensen 1997) or *socially desirable* innovations serving long-term societal goals (such as ecological sustainability) - both of which face a mismatch and misalignment with regard to existing infrastructures, regulations, and practices - the notion of technological niche refers to a "protected space that nurtures a specific set of interactions" (Schot and Geels 2008; see also Rip and Kemp 1998; Law and Callon 1988) and allows for the "experimentation with the co-evolution of technology, user practices, and regulatory structures" (Schot and Geels 2008), in a way conducive to making a technology and society mutually acceptable (Schot and Geels 2007). In other words, innovation niches are constructed spaces, sheltered from mainstream competition while different in shapes and sizes[9], where the (technical) content and the (societal) context of innovation can be reciprocally adapted, thus reinforcing the consolidation trajectory of innovative technologies and practices[10]. As such, the notion of niche allows for the development of an analytic perspective attentive to both the role played by the context in influencing the dynamics or 'journeys' (Van den Ven et al 1999) of

[9] An example of niche could be the test lab for new products, functioning as a domesticated selection environment, where the risks of selection occur in private (see Rip 2012).

[10] More in detail, SNM scholars (cf. Schot and Geels 2008) have argued that, within technological niches, novelties emerge through internal, bottom-up processes (akin to inner-platform dynamics) revolving around: (i) the articulation of expectations and visions, providing direction and guidance to the development of niches, and (ii) the construction of a robust social network, that creates a constituency behind the new technology by facilitating the enrollment and mobilization (Callon 1986) of relevant stakeholders, while fostering learning processes at multiple dimensions (concerning the technical design of the technology, users preferences, the regulatory landscape, etc.).

innovation, and the way in which, conversely, emerging innovations lead to changes in their underlying social context.

At the same time, however, inasmuch as it maintains a narrow focus on small-scale networks and socio-technical configurations being molded around specific emerging technologies, the notion of niche is unable to capture the "general patterns and structures in the context, relevant to innovation dynamics, over and above the specific constellation of actors and framework conditions at play in the particular innovation journey that is considered." (Rip 2012). In other words, identification of relevant niche-internal processes is not enough to fully tease out the manifold forms of mutual interactions in play between the content and context of innovation. As Schot and Geels (2008) observe, building on this line of analysis:

> *it is clear that internal niche developments are not the only important factor. External factors also play a crucial role. Niche innovations are rarely able to bring about […] transformation without the help of broader forces and processes. This conclusion led to a search for conceptualizations that linked niche internal and external processes. This search was done under the heading of the multi-level perspective.*

Accordingly, this analytic perspective, mostly owing to the work of Arie Rip, René Kemp and Johan Schot (Rip 1992; Rip and Kemp 1998; Kemp, Rip and Schot 2001), has developed a *multi-level* model of innovation, focusing on both *internal* processes propelling the expansion of technological niches, as well as *external* processes that contribute to the broader societal diffusion of niche innovations. More to the point, this analytic framework operates a three-layered partition of the "space" of innovation, distinguishing between the *macro-level* of the socio-technical landscape, the *meso-level* of the socio-technical regime and the *micro-level* of the technological niche. The

*technological niche*, whose tenets I have briefly expounded above, is where radical *novelties* emerge. The *socio-technical regime* carries and stores rules (both cognitive routines and belief systems, as well as regulative rules and normative roles) for how to produce, use, and regulate specific technologies (Schot and Geels 2007, 2008); as such, it accounts for the *stability* of existing technological systems – which, in turn, could make innovation difficult to introduce. The *socio-technical landscape*, "the slowly changing backdrop against which interactions are played out" (Rip 2012), represents the exogenous environment, in both a literal (the surrounding space) as well as metaphorical sense – a *repertoire* (Gilbert and Mulkay 1984) of norms and values (Rip and Kemp 1998); it comprises those elements beyond the direct influence of niche and regime actors, such as deep cultural patterns, political and macro-economic developments, institutional configurations.

Building on this analytic partition, the multi-level perspective on technological change emphasizes how interactions and alignments between processes at different levels are needed to bring about transition: not only do technological niches exert pressure "from below" on established socio-technical regimes; changes at the landscape level create pressures on regimes as well, thus creating "windows of opportunities" for niche innovations to emerge and consolidate themselves. This process of mutual interactions could be eventually conducive to adjustments, or even reconfigurations, at the regime level, something that could then exert influence on the landscape itself in a recursive dynamic.

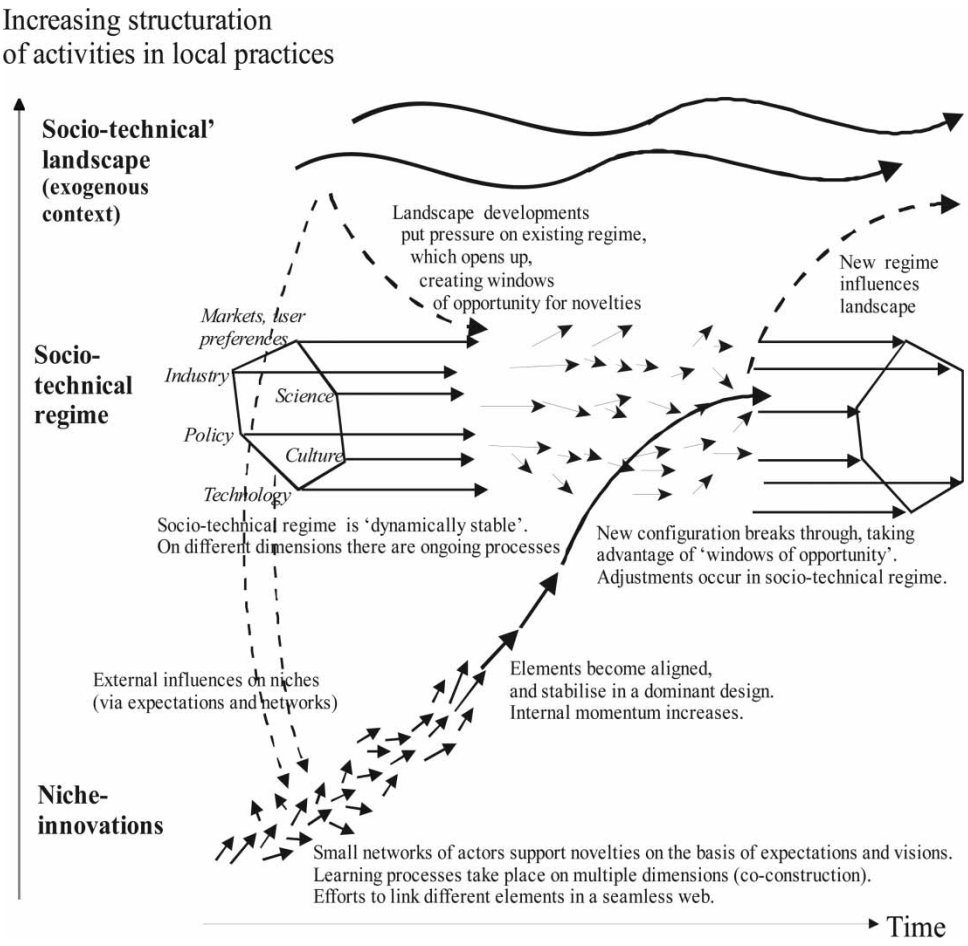


**Figure 7: Multi–level perspective on technological change (adapted from Figure 5 Schot and Geels 2008)**

The key idea in play here, in other words, is that technological change takes place through processes of "co-evolution and mutual adaptation within and between these layers" (Rip and Kemp 1998). Therefore, rather than bestowing explanatory power to either niche, regime or landscape configurations, this analytic framework identifies mutually-sustaining *interactions* and *tensions* occurring at the niche-regime-landscape *interface* as the privileged site of analysis to account for both the exogenous and contextual forms of influences that contribute to a technology stabilization, and its performativity in the broader socio-political landscape (i.e., how niche-dependent innovations either manage to successfully challenge established socio-technical regimes; or become incorporated and normalized (May and Finch 2009) into existing regimes; or, again, set in motion a series of developments that result in changes to the landscape itself).

### 3.5 Probing platforms in context. The *exogenous co–production* of networks of knowledge and socio–political orders.

While not exhaustive of the hefty literature on SNM and the multi-level model, these remarks can serve well as analytic pointers to be used in order to shed light on some of the (under theorized) 'exogenous' dynamics occurring at the platform-context interface, and can be thus be brought to the task of analyzing the emergence and consolidation of platforms, as well as the performative role they play within their underlying socio-political context.

In particular, they point to how the entrenchment of platforms is heavily reliant on the relations they entertain with the outer context (that provides both resources and constraints for their development), i.e. the broader socio-technical landscape comprising the national political cultures (Jasanoff 2005) with their institutions; the national and global bio–economies and market configurations; the international regulatory spaces created within specific *technological zones* (Barry 2006); the *adoption spaces*[11] (Ulucanlar et al. 2013) in which technologies are mobilized, while also being framed in a particular way that define how they are perceived by users and the public (as being, for example, 'novel', 'revolutionary', 'prestigious', or 'difficult to implement', 'risky' and so on).

Drawing from this perspective, I am thus able to identify, in conclusion, a second way in which the co–productionist framework can be deployed in relation to the notion of biomedical platforms to account for the mutual constitution of epistemic and normative orders. Accordingly, I argue, that reprogramming-based platforms are conspicuous examples of a higher, meta-level of 'reprogramming', through which platforms are sculpted by and in turn re-shape their broader socio-political context, and that I propose as an *exogenous* form of *co-production*.

[11] Ulucanlar and colleagues (2013) define the adoption space as the context "where attitudes, practices, interactions and events, together with the technology's material features, shape technology perceptions in ways that are instrumental in decisions about its use."

On the one hand, translation–oriented biomedical platforms are an important vehicle to advance and materialize visions of desirable futures and normative stances, concerning social order and the collective good (see chapter 1), in ways that will be empirically probed in the following chapters of this dissertation. For instance, as the paradigmatic case study of the European Bank for induced Pluripotent Stem Cells (EBiSC), analyzed in chapter 6, vividly attests, they not only *encode* and *reinforce* (Jasanoff and Kim 2009) particular conceptions of what a (supra)national entity, such as the European Union, stands for; but also, in the context of contemporary knowledge–based societies, where human cells have been increasingly replacing coal and steel as the main threads in the fabric of economic development and political integration, they are enrolled in projects of *(supra)nation–building*, thus representing privileged means deployed by institutional actors for forging new economic and political identities.

At the same time, as most clearly elucidated by the two American case studies of NYSCF and HSCI, analyzed in chapters 4 and 5, the emergence of innovative platforms navigating an enticing scientific field does not simply fall along established socio-political boundaries but redraw them in significant ways, in what Ruha Benjamin has aptly called the "co–emergence of cellular and civic configurations" (Benjamin 2003). For, while operating in the same scientific field within the same socio–political context, NYSCF and HSCI uphold distinct framings of the constitutional position of science in society (Jasanoff 2012), thus contributing, through their endeavors, to the emergence and reinforcement of distinct, and in many ways competing, socio–political orders. Sheila Jasanoff (2012), in one of the most poignant pieces of her scholarship, argued that:

> *Networks of new knowledge and its material embodiments are helping to frame and stabilize some of the basic elements of a global political system, such as the rights, privileges, and identities of the world's citizens and the powers of major global actors. I have argued that the totality of these changes is constitutional in scope, both enabling and constraining new political formations. Through science and technology, seen as*

*profoundly social institutions, many parts of the world today are engaging in what amounts to a tacit constitutional convention. On the table are the nature of the human self, the relations of consumers and corporations, and the certification of knowledge in the conduct of global politics.*

How the emergence of innovative iPSC research platforms, coalescing around specific configurations of actors advancing distinctive normative agendas, is brought to bear on the broader socio–political landscape they inhabit, is thus another major theme that I seek to address in the following chapters of this dissertation.

# Chapter 4. The New York Stem Cell Foundation.

## 4.1 From federal politics to stem cell research platforms.

As Herbert Gottweis has poignantly observed, "from a discourse-analytical perspective one important aspect of policymaking is the fact that it is always a performative process that uses and mobilizes complex and often heterogeneous systems of representation to fix the meaning of transient events" (Gottweis 2002). As such, policymaking performs a fundamental signifying and ordering function, insofar as it does not simply *react* to the emergence of novel biomedical entities, technologies, and research practices assumed as "objective data" (*ibid.*) for regulatory decision making, but rather, it actively *inscribes* the normative stances it advances into their textures, thus *constructing*, as well as *controlling*, the latter's material and socio–political ontology (Jasanoff 2005).

As the case of NYSCF and HSCI vividly attests, the stabilization of the stem cell research field in the United States owes indeed, in large part, to well-known and widely debated developments in the recent past of that country's politics. NYSCF and HSCI were established as paradigmatic - yet distinctive - byproducts of a broader process of boundary work (Gieryn 1999) by the federal science policy that, at the onset of the 21st Century, set and stabilized new boundaries between stem cell science and the polity, while decisively contributing to the shaping of the nascent field of human pluripotent stem cell research.

The stabilization of the scientific-political domain of stem cell research, in particular, was strongly influenced by the "mobilization of historical narratives" (Gottweis 2002) derived from past struggles over embryo and fetal research[1], in which the latter, far from just being matters for concern *per se*, or insofar as they could foster ancillary and possibly

[1] Notes Gottweis (2002) that "central in these debates was the question of what constitutes an embryo and a fetus and thus – implicitly – at which point in the reproductive development "life" comes into existence. Also important were the potential socio–cultural and moral implications of fetal and embryo research and the role of the law and the state in the "protection" of embryos and fetuses."

morally repugnant practices, such as abortion or selective breeding of embryos for research and therapeutic purposes (Jasanoff 2005), were, "from the start, a salvo in national and international political debates about innovation, abortion, and competition in ways that were over-determined and under-situated, with bioethics as a lingua franca zone of contestation" (Thompson 2013).

In what follows, I thus aim to carry out a twofold task, reviewing the most salient junctures in science policy leading to the current configuration of the stem cell research field in the United States, while also sketching out some of the underlying political narratives attending to its stabilization. As a word of warning, such brief review, as any genealogical reconstruction, is partial and situated. Rather than aiming to attain a supposed objectivity, something that both philosophers of history and STS scholars have long since recognized as an elusive feat (Derrida 2013; Haraway 1988), I intend to chart some of the milestones underpinning the consolidation trajectory of the field of stem cell research, thus providing a socio–political contextualization for the establishment of the stem research platforms I analyze in the subsequent part of the dissertation.

### 4.1.1 The Clinton years.

Arguably, a good starting point to map out the evolution of the science policy landscape concerning embryo and stem cell research in the US political context can be dated back to the dawn of the Clinton Administration. In 1993, with the NIH Revitalization Act (NIH 1993), Congress and President Clinton devolved to the NIH, for the first time, direct authority to fund human embryo research. In practice, the Act abolished the need for such a research to be approved by the NIH's Ethics Advisory Board, as required by the Federal Policy for the Protection of Human Subjects enacted in 1977. As such, it reversed what, if not *de iure*, at least *de facto*, represented a ban on the federal funding of embryo research: as it went, when the Ethics Advisory Board charter expired in 1980, no renewal or

replacement body was put in place by Congress, so that research proposal had nowhere to go for review, and no federally funded research could hence have been made possible (Salter, Gottweiss, Waldby 2009). Meanwhile, in the same years, privately funded embryo research was left relatively unencumbered (Kinner 2000), in a way that established a "clearly drawn boundary" (Gottweiss 2002) between public and private research for the emerging space of embryo and fetal research[2].

In 1995, however, Republican-controlled Congress reversed that position and approved what came to be known as the Dickey-Wicker Amendment to the appropriations bills for the Departments of Health and Human Services, Labor, and Education for Fiscal Year 1996. An important and perduring piece of legislation, having being renewed each year through Fiscal Year 2009, the Amendment dictates that US Government funds cannot be given to research that "directly *makes*, *destroys*, *discards* or *harms* any living human embryos" (P.L. 104-99). It hence erects barriers to using federal funds for research that included creating stem cell lines from embryos and embryo-like organisms.

The Clinton administration's pushback arrived in August 2000 when the NIH published new guidelines, following the first derivation of hESC lines by Jamie Thompson's laboratory in 1998, and the mobilization of ontological politics (Mol 1999) in the form of a legal opinion issued by the Department of Health and Human Services, creating a line of demarcation between hESC lines and embryos by stating that the former "are not a human embryo within the statutory definition" (DHHS 2000, quoted in Saul 1999). Against this backdrop, the new NIH guidelines forbid the use of federal funds to destroy human embryos to derive stem cells (in line with the provisions of the Dickey-Wicker

[2] In parallel, it should be noted how, on the contrary, *ex utero* fetal tissue (from aborted fetuses) has been the subject of research since the 1930s (Kinner 2000b), with NIH funding being made available since the 1950s, a decision being reversed in 1988 by the Reagan administration. As noted by Gottweis (2002), "the central argument of the critics of fetal research in the Reagan and Bush administrations was that research needed to be terminated. Otherwise, there could be a chance that women might feel encouraged to have abortions because they might see a chance that their abortions could be useful to tissue recipients".

Amendment), but permitted research with stem cell lines derived from IVF spare embryos slated for being discarded at fertility clinics.

### 4.1.2 The Bush years.

On the backdrop of a controversial electoral victory that enabled the advancement of a 'compassionate conservatism' agenda in many respects aligned with that of the religious right, in August 2001 the Bush Administration enacted policy, "expeditiously implement[ed]" by the NIH (NIH 2001), that brought the federal funding of human embryonic stem cell research to a virtual standstill[3]. The Bush administration's policy required indeed that federal funding for hESC research should be restricted to research using stem cell lines that met a number of criteria (stemcells.nih.org): (i) the derivation process (beginning with the "destruction" of the embryo) had to be initiated prior to August 9, 2001; (ii) the stem cells must have been derived from an embryo that was created for reproductive purposes and was no longer needed; (iii) donation of the embryo must not have involved financial inducements, and informed consent must have been obtained. 71 lines from 14 laboratories worldwide (the so called 'presidential lines' established within the NIH registry soon thereafter) met Bush's eligibility criteria, although only 21 lines were deemed experimentally viable by the scientific community (Murugan 2009).

Yet, while restricting federal funding, the Bush policy still adhered to a well-rehearsed libertarian policy script, dating back to the 1970s (Khushf 1997), that no overall, *tout-court* ban on research practices involving embryos or fetuses be imposed (Salter, Gottweiss, Waldby 2009). The rationale underpinning the Bush administration's ruling - in many ways consistent with the previous policy of the Clinton Administration, in that combined support

[3] Noted for instance a HSCI scientist involved in hESC research at the time (Lensch 2008), that "the current policy demands that when working stem cell lines created after August 9, 2001 (2), I cannot use existing (and often expensive) equipment that was purchased using NIH money for what otherwise may be identical work. This means that I have to have separate centrifuges and microscopes for cell A versus cell B, different pipettes for culturing cell A versus cell B, and even a different pencil for taking notes on cell A versus cell B, thus wasting money, space, and time."

for research with elements of restriction (Salter, Gottweiss, Waldby 2009) - was influenced considerably by the longstanding "right-focused discourse" about the regulation and public funding of non-therapeutics abortions in the US (Gottweiss 2002). The absence of public consensus regarding the moral status of the (pre)embryo, so the reasoning went, argued against both the development of regulations constraining research and the use of public funding to support it, as "the liberty or resources of some individuals would [have been] inappropriately constrained or co–opted to pursue ends that they would explicitly eschew" (Khushf 1997).

Hence, as the ruling did not affect private investors and individual states alike, a twofold boundary was created and enacted (Thompson 2013), demarcating the public from the private, and states from the nation, as a source of funding, steering and governance for hESC research – with wide–range implication for the configuration of American stem cell research that reverberate well into the present decade (see below).

### 4.1.3 The Obama years.

During the Bush presidency, the ban on the federal funding of hESC research was repeatedly challenged by both Republicans and Democrats, in line with growing popular support for such kind of research (Thompson 2013). In 2005 and 2006, similar bills that would have made federal funds available for hESC research on "leftover" embryos, following appropriate consent by donors (i.e. the Stem Cell Research Enhancement Act of 2005, H.R. 810), were approved in the House and the Senate, only to be vetoed by President Bush. Furthermore, on June 20, 2007, following another presidential veto of measures lifting restrictions on human embryonic stem cell experimentation (i.e., the Stem Cell Research Enhancement Act of 2007, H.R. 3) (Stolberg 2007) - the third of his presidency and the second on the topic of stem cell research - President Bush issued

Executive Order 13435 that, while making significant rhetorical changes[4] (Thompson 2013), *de facto* upheld the 2001 federal funding ban.

Similarly to the importance attributed to the issue by his predecessor, who devoted to stem cell research his first Presidential Address to the nation from his ranch in Crawford, Texas, on August 9, 2001, one of the first pieces of legislation crafted by newly appointed President Obama was the promulgation, on March 9, 2009, of Executive Order 13505. Titled "Removing Barriers to Responsible Scientific Research Involving Human Stem Cells", the executive order revoked the Bush–era policy of August 9, 2001, Executive Order 13435 of 2007, and charged the NIH with the task of developing guidelines for the funding of human pluripotent stem cell research (Thompson 2013). In summary, the main change was to permit the use of federal tax dollars for research on hESC lines that had been derived from leftover IVF embryos, whether or not they had been derived before August 9, 2001.

With the advent of the Obama presidency, and the contextual emergence and consolidation of iPSC research (the first human iPSC lines were derived at the end of 2007), the field of stem cell research underwent a rapid process of consolidation. Whilst conducive to the normalization of relationship between stem cell science and the American polity, this process brought about a twofold relevant implication.

On the one hand, it made more difficult, for research organizations that grew accustomed to rely on private funding as their main form of sustenance, to tap into the same wealth of resources that were in fact previously mobilized, other than for support of

[4] As Noted by Thompson (2013), "first, the NIH's registry of stem cell lines eligible for federal research funds, formerly known as the Human Embryonic Stem Cell Registry, was renamed the Human Pluripotent Stem Cell Registry. Second, the order articulated Bush's deontological principle in a clearer way, refusing the sacrifice of one life for the medical benefit of another […]. Additionally, the order linked Bush's positions on embryo destruction to concerns about the commodification of humans – a less partisan issue because of its appeal to many progressives and many religiously motivated voters – by defining embryos as part of the human species[.]"

stem cell research itself, as political statements against the policies of the Bush administration. Noted the CEO of a major American stem cell research organization that,

> *At the beginning, it was a lot easier to raise funding, when people during the federal ban wanted to support work that wouldn't have been supported otherwise. […] Moreover, at the very beginning, I would say a lot of people were angry at the President, and at the politics. And in fact, that was a bit of a challenge for us because when we didn't have a bad guy any more, it was like "wait a minute, why am I still supporting [the organization]?"*
>
> Interview with CEO, stem cell research organization

On the other hand, and most relevantly, such normalization diminished the level of public attention, political scrutiny, and ethical oversight devoted to the field of human pluripotent stem cell research – a field and a science that, precisely because of such inseparable entwinement of the *technical* and the *normative* underpinning their standardization, was accustomed, in the words of Charis Thompson (2013), to "have ethics"[5]. For instance, notes Thompson (*ibid.*) with regard to the case of the California Institute for Regenerative Medicine (CIRM), "everyone was working to remove the use of somatic cells for iPS experiments from high levels of scrutiny. Now iPS research required SCRO notification only if using identifiable cells, and the lowest level of oversight (a statement compliance) if using de–identified cells, even if they came from fetal tissue". In a way, I contend drawing from Thompson (2013), these developments not only contributed

[5] Thompson (2013) writes: "I use the word 'ethics' in this book to refer to the wide-ranging activities including formal bioethics policymaking, in which various actors engaged during my research (myself included) to advocate for some ways of proceeding with pluripotent stem cell research over others on the ground that they would be better for some people or things in some ways. As such, ethics is an overarching normative term for me, ranging in its application from political contests over funding, rhetoric, and institution building to matters of personal belief and normative arguments made by scholars and activists mailing from a range of disciplines and social locations. […] The ethics of sciences that 'have ethics' can be contrasted with a more conventional view of the ethics of science made up of a professional code of conduct (don't fake your results, don't steal my reagent) and possible downstream ethical, legal, or social implications (after the science is over, are the results used for good or ill?)".

to overshadowing other relevant biopolitical issues related to stem cell research[6], but also *reinforced* the consolidation of *privatized regimes* of innovation (analyzed below in relation to NYSCF and HSCI's endeavors), whose emergence owes, in the first place, to the enactment of President Bush's 2001 federal ban.

### 4.2 Narratives and policies.

Among all the twists and turns, some consistent "discursive codes" (Gottweis 1998) and narratives shaped the consolidation of the science policy context underpinning the establishment of the stem cell research platforms analyzed in this dissertation.

As a legitimacy strategy meant to both elicit and justify support for a high controversial field of research, and counterbalance pro–life objections to it, the narratives of both the Clinton and the Obama administrations, as well as of the wide plethora of actors supportive of stem cell research, mobilized two core elements of the US political identity, American health and American scientific and technological leadership, and tightly linked them to hESC research policy (Gottweis, Salter and Waldby 2009). Stem cell research thus became a proxy of, and an "extended promise" (*ibid.*) for, the future of both the well–being of citizens, medical research, and the technological primacy of the US on the world's stage. As, for instance, President Obama remarked in his signature rhetorical fashion in his March 2009 speech, preceding the promulgation of his Executive Order:

> *This Order is an important step in advancing the cause of science in America. [...] By doing this, we will ensure America's continued global leadership in scientific discoveries and technological breakthroughs. That is essential not only for our economic prosperity, but for the progress of all humanity.*

[6] Following Thompson (2013), I use the term 'biopolitics' in the broad sense as encompassing questions about "who lives at whose expense through which technics". Marginalized biopolitical questions of such kind thus concerned the relation between the funding of stem cell research and issues of inequalities in healthcare access; the tensions between the emphasis on technological innovation and other aspects of disability justice; the research subjects and the donors of tissue samples; the 'dual use' of stem cell technologies in military research (see *ibid.*).

As Charis Thompson has poignantly observed (2013), stem cell research in the US context has thus been propelled and supported by a *pro-cures-as-innovation vision*, i.e. a rhetoric that bundles together "the fundamental ethical imperative to save and improve lives" and biotechnological innovation. Put otherwise, the legitimacy strategy of those who, moving at different scales (from federal to state politics, to single research organizations), sought to articulate the normative commitment to advance stem cell research against ethical, religious, and political objections, hinged heavily on the mobilization of the *translational narrative* (analyzed in chapter 1) revolving around the twofold *curative* and *economic* potential that stem cells would hold, in healing the wounds of the diseased patients as well as those of an ailing post-fordist economy. Observes Thompson (2013), with specific regard to the case of California and the state–funded CIRM (but her observation can be easily generalized):

> *To make plausible this ethical claim that the point of research was cures, the research had to be shown to be concerned with the entire innovation trajectory, all the way from as–yet–undone basic science to clinically valid treatments. The bench–to–bedside commitment also lent itself to being read as a commitment to funding a new field of innovation, putting California out ahead of the rest of the US and even the world. State investment in this "next Silicon Valley" had the potential to reinvigorate California's economy; the research might also dramatically cut medical costs currently incurred by dealing with chronic conditions that might be cured with stem cell research.*

Secondly, while the Clinton, Bush and Obama administrations' policies varied with regard to their practical outcomes, as well as the framing of both the ontological status of embryos and the ethical implications of hESC research – according to the distinct meta-ethical positions and political worldviews they upheld – they nevertheless adhered to the longstanding libertarian stance concerning the regulation and public funding of non-

therapeutics abortions, whose central argument was that the absence of public consensus regarding the moral status of the pre-embryo excluded both the development of regulations constraining embryo–based research and the use of public funding to support it.

As noted above, such stance played a critical role in enacting and legitimizing the creation of a boundary between the *private* and *public* in the field of embryo research – in stark contrast to developments occurring in other political contexts, where the demarcation between allowed and forbidden research was traced along different lines, such as the embryo's country of origin[7], its development stage[8], or its derivation methods[9] (see e.g., EuroStemCell.org, Jasanoff 2005, Metzler 2011, Testa 2011).

On the backdrop of these developments, the growth in significance of constituencies not accustomed to be science policy leaders in the US (Thompson 2013) triggered significant experimentation in science policy: those empty spaces opened up by the retreat of the federal *government* from a key area of biomedical innovation had to be filled by innovative and more flexible regimes of *governance* (Nowotny and Testa 2011), advanced by new biomedical collectives tinkering with new norms, standards and forms of regulation.

As a new socio-political geography of biomedical research was established, the pressing issue that had to be confronted by these emerging collectives - notably, among them,

[7] In Germany, in line with the provision enacted by a 2008 amendment to the 2002 Stem Cell Act (Stammzellgesetz), the derivation of embryonic stem cells is banned, but embryonic stem cell lines can be *imported* specifically for research if the line was generated before the cut-off date of May 1, 2007 (the date originally defined by the 2002 act was January 1, 2002).

[8] In the UK, research on human embryos is regulated by the Human Fertilisation and Embryology Act (1990) and the subsequent Human Fertilisation and Embryology (Research Purposes) Regulations 2001, and can only take place on embryos up to 14 days.

[9] In Italy, the Dulbecco Committee set up by then Health Minister Umberto Veronesi in 2000 stated that stem cell lines could be derived from SCNT–derived clones, but not from IVF–derived embryos. As poignantly observed by Giuseppe Testa (2011), the provision of the committee represented an "ontological exercise in kind–making", for it was the first time that a political body framed "clones as distinct from embryos". The words of the Dulbecco Report, whose provisions were overturned by the subsequent approval of Law 40 in 2004, are surely worth reporting: "An enucleated oocyte reconstructed with an adult somatic cell nucleous cannot be considered as a classical zygote, because it does not derive from the union of two gametes. This is proven by the fact that such a reconstructed oocyte does not develop spontaneously into an embryo, and this happens only following artificial stimulations that force it to develop into a blastocyst. Only few of these blastocysts possess the effective capacity of forming an embryo, and hence a fetus, once transferred into the uterus. […] Finally, the oocyte reconstructed with a somatic cell nucleus is much more similar to a potential form of asexual cellular expansion of the patient, in analogy to what is currently practiced when skin biopsies are amplified in vitro" (DC 2000).

academic centers established at elite universities such as Harvard, MIT, Stanford; non-profit organizations such as NYSCF; state-sponsored agencies and funding programs such as the California Institute for Regenerative Medicine (CIRM) - was to carve out their own space of public legitimacy. To this end, they engaged in a comprehensive process of framing (Jasanoff 2005), mobilizing narratives supporting the distinctive models of innovation being designed and implemented, while recasting competing visions of the scope and aims of 'good' stem cell science (e.g., the way stem cell research operates, under whose responsibility, and towards what ends; how agency and resources are allocated among actors; how epistemic and financial risk, as well as ethical controversies inherent to lines of research being pursued, are assessed and managed).

In this context, the subsequent advent of iPSCs has *reinforced*, rather than *challenged*, the governance models initially developed by these stem cell platforms around hESC (and, to a lesser extent, SCNT) technologies. In what follows, I thus move *in medias res* and investigate how, through the establishment of distinct regimes of governance and innovation strategies, HSCI and NYSCF – the two American stem cell organizations I analyze in this dissertation – *distinctively* reproduce and recast the commitment to advance translational stem cell research, while insulating it from "unwanted" political pressures.

## 4.3 A "New Research Model" to Accelerate Translational Stem Cell Research: The New York Stem Cell Foundation.

> *I was asked whether I wanted to participate in writing about The New York Stem Cell Foundation as a case study... Can this model be exported on a broader level? I think it's a good idea, and it can, and it should. It's because the independence, the integrity of the entrepreneurial engine... it's really a pure model, because to be able to do the best work with the best people, and not have to pay the piper of a study section, or a commercial interest, is what has allowed us to have I think eight of the major innovations in the entire field, and we have only been around for nine years! There is definitely something in the air,*

*a sort of secret sauce, and you see it when you come to the lab - it's like a parallel universe, everyone is really happy!*

Interview with CEO, NYSCF

The origin of the New York Stem Cell Foundation as a "parallel universe", in the poignant words of its co-founder and CEO, dates back to the Summer of 2005 and owes mostly to the charismatic leadership of Susan L. Solomon, a former attorney, venture capitalist and entrepreneur–turned–patient advocate following her son's type I diabetes diagnosis.

In the political climate of the time, and following in the footsteps of early pace-setters such as Harvard University (see chapter 5) and the State of California, which established the $ 3 billion-funded California Institute for Regenerative Medicine (CIRM) in 2004 (Hayden 2008; Benjamin 2013; Thompson 2013), Solomon started engaging in conversations with fellow patients advocates and leading figures in biomedical research, such as Harold Varmus (former director of NIH under President Clinton) and Nobel Prize laureate Paul Nurse, with the intent of setting up a stem cell program in New York City. Tapping into her extended advocacy and business network, she soon accrued an initial capital of $ 1.7 million (which rose to more than $ 120 million by 2014 (Solomon 2012a, 2012b; field notes 2014)) and set up a non–profit organization from scratch, operating at first from the living room of her luxurious Upper West Side apartment in New York City – thus adding a little twist to a well–worn cliché of American innovation – before moving, in 2006, to the premises NYSCF currently occupies in the same district of the city (field notes 2015).

Therefore, similarly to other endeavors driven by the thrust of single, or a small group of typically wealthy and well–connected individuals (see e.g., for the case of the CIRM, Thompson 2013; Benjamin 2013), the *biographical* and *political* elements knitted together to propel the establishment of the organization. If the diagnosis of her son with juvenile

diabetes represented, for NYSCF's CEO, "an unwanted visitor in your home" giving "a personal sense of urgency" to her advocacy (Solomon 2012; interview with CEO, NYSCF), the Bush administration policies were equally perceived as an unwarranted hindrance – both of them prompting action to "move ahead as quickly as possible [to] put together a private organization supported by philanthropy" (interview with CEO, NYSCF).

### 4.3.1 The beginnings.

The decision to establish NYSCF hinged on two aspects perceived as equally crucial by Susan Solomon and the small group of philanthropists and patient advocates involved in the first steps of the organization, namely the lack of government support for embryonic stem cell research, and the perceived lag in the commercialization of academic research findings. Therefore, since its inception, NYSCF moved swiftly in order to pursue two key objectives.

The first priority was to support the hESC field, deemed in danger of not surviving its infancy due not only to lack of funding at a critical stage of its development, but also to the threat of promising researchers being "scared away towards safer havens" by regulatory burden (interview with CEO, NYSCF). Recalled the CEO of the organization that "one clear problem was that because of funding policies in the USA at the time, young researchers were discouraged from going into the field. So we thought it was very important to establish a well-supported community, as quickly as we could. We wanted to help early post-doctoral researchers: fund them, give them ways to collaborate, and support from top people in the field, so that they could be encouraged to go into the field" (Solomon 2012b).

Accordingly, NYSCF set out to establish an extramural research granting program, aimed at providing funds for cutting–edge research conducted by (early career) investigators all over the US, as well as to host a major translational stem cell conference in Manhattan, with the intent of "bang[ing] a drum loudly" (Solomon 2012), raising

awareness for stem cells and hence funnelling public support and resources towards this emerging field of research and the organization itself. As explained by the CEO:

> *we needed to wake people up: this was a very exciting, emerging field, and they need to take time off their busy schedule and pay attention. The 'they' were researchers, clinicians, and opinion leaders of all sorts. So it was decided that we would have had a major annual conference (that we hoped would have become a leading conference), and for the last nine years we held a big, annual translational stem cell meeting.*
>
> Interview with CEO, NYSCF

Notably, other than to report NYSCF–sponsored scientific breakthroughs and promising lines of research to the broad scientific community, the launch of the annual conference – with its well–attended, close–door gala dinner, which gathers, among the invited guests, many top Wall Street executives (Gordon 2015) – was also aimed at showcasing the organization to potential donors, thus fuelling a "celebratory culture" – out of which NYSCF thrives – which is "functional to the raise of funding in competition with other major stem cell organizations" (interview with NYSCF investigator).


**Figure 8. Photo taken at NYSCF's 9th annual Translational Stem Cell Conference, held at Rockefeller University, October 22–23, 2014.**

As a means to further support promising, albeit hindered, lines of research, in 2006 NYSCF decided to set up its own research facility in Manhattan's Washington Heights, a site that has meanwhile grown more then tenfold since its inception, and now employs over 45 researchers. Conceived as a "safe haven laboratory", the facility was intended to insulate stem cell research from fluctuations in political support and federal funding, so as to enable its unrestrained pursuit. In the words of the CEO,

> *we felt it was really critical […] to have a place where the work could happen and you could check the politics at the door. And we still think that this is really, really important.*
>
> Interview with CEO, NYSCF

Curiously, the prompt for establishing the laboratory did not come from hESC research itself, but rather from an equally contested, albeit less developed, line of research, that on SCNT. Recalled the director of scientific programs and the chief of staff of the organization (field notes 2014 and 2015) that, in 2006, scientists in two leading East Coast universities, Harvard and Columbia, were intending to set up a collaboration on a line of research involving the derivation of patient–specific stem cell lines by means of SCNT from diabetes patients, with the primary goal of better understanding the biology underpinning the disease, and the longer–term aim of possibly developing cell–based therapies. Since, however, the Bush administration's policy prevented SCNT research to be conducted within federally–funded premises, thus severely hindering the development of this line of research, scientists at the two organizations soon realized that they needed a shortcut, and reached out to NYSCF in order to get out of the impasse. As remarked by the director of scientific programs:

> *None of the universities were basically able to do this within their campuses. They needed a safe haven lab, and asked Susan if she was able to set it up, and she did. It*

*started with a room where all they did was SCNT. Over time other people wanted to access a safe heaven-type of laboratory, and it started to evolve a bit.*

Interview with director of scientific programs, NYSCF

**Figure 9. NYSCF's research facility in Manhattan's Washington Heights.**

### 4.3.2 Bridging research and cures.

Other than supporting hESC and SCNT research, the second, equally critical objective pursued by the organization was to enable a distinctively translational research pipeline. Accordingly, since its inception – and even more so after the derivation of human iPSCs in 2007 – NYSCF's *organizational culture* (Schein 1984) was based on a translation–oriented approach, one in which the creation of a shared professional identity among members of the organization (i.e., its *internal integration*) and the definition of the tasks to be

accomplished, and the methods to reach the goals (i.e., its *external adaptation*), proceed from the translational mandate.

In particular, consistent with its ambition to "accelerate cures for the major diseases of our time through stem cell research" (mission statement), NYSCF implemented a specific organizational gearshift revolving around two mutually-sustaining pillars. First, in setting forth its research objectives, NYSCF marked an explicit departure from academic orthodoxy, foregrounding therapeutic innovation over traditional peer recognition. As a staff scientist explained:

> *We don't care much about the papers that come out of our lab, as the process of obtaining enough data on a drug to move into the clinic is very different from generating enough data to publish a Nature paper, and what we are focused on here is to take one of our discoveries and get funding for it to move it fast along the translational pipeline.*
>
> Interview with staff scientist, NYSCF

Furthermore, in devising its organizational model and establishing its experimental infrastructure, NYSCF set out to target and address a perceived major impediment to the effective translation of biomedical research, namely the "giant gap between the work being done at academic institutions, and the delivery of pills and treatments on the commercial side" (Solomon 2012b). In particular, in order to accelerate access across academic and private sector parties, the leadership of the organization sought to carve out for NYSCF the role of the (gap-remedying) *mediator* (Latour 2005), one that could streamline the *transmission* of scientific knowledge from academia to the industry by attending to its quintessentially material *transformation* - i.e., *translation* - into fungible, clinically actionable products. In the words of NYSCF's director of scientific programs:

> *We try to see ourselves as a translational component in between academia and biotech or pharmaceutical companies, some sort of an accelerator. […] In fact, in one*

*aspect, we already are one of the biggest players in the field, not the largest stem cell lab, but we are the most focused on translation and scale up of any group in the world in stem cell research.*

Interview with director of scientific programs, NYSCF

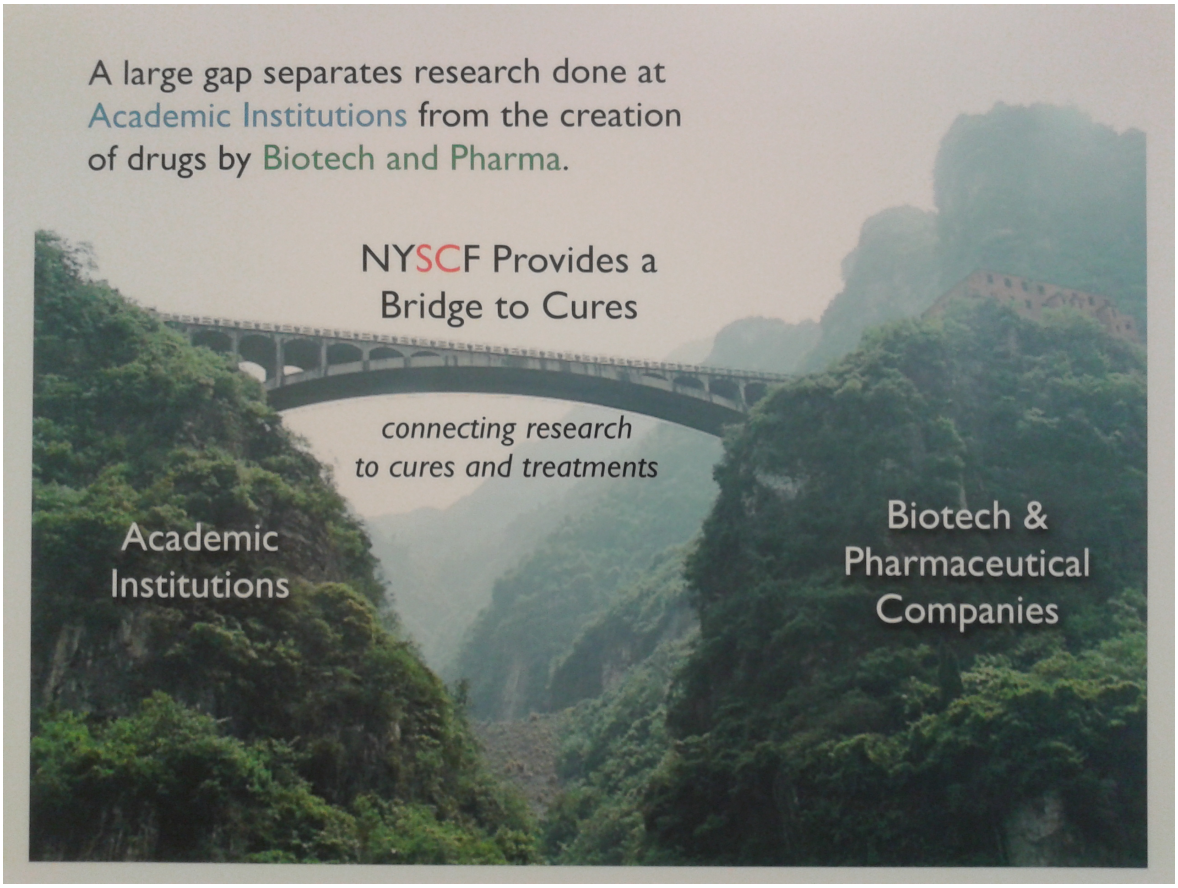


**Figure 10: NYSCF's self-portrayed role as translational component in between academia and pharmaceutical companies (photo taken at NYSCF laboratory by LM)**

More to the point, vis–à–vis the purported chasm disconnecting 'research' from 'cures and treatments' (as for NYSCF's own rendering of the 'valley of death' metaphor, see Figure 3), NYSCF adopted a *centralization strategy* aimed at establishing, within its own research laboratory, those translation-grade infrastructures that the field was deemed to be lacking in order to create efficient synergies and linkages between academic and pharmaceutical research centers. Most notably, as described in detail below, NYSCF devoted a significant amount of time as well as cognitive and material resources towards designing and establishing the largest robotic device for iPSCs derivation, culture and

differentiation in the US, which came to represent the cornerstone of its translational pursuit, as well as the organization's poster child for its aggressive marketing strategy with potential donors. Less glamorous but equally relevant, it also devised a consenting form, "which now is widely used by the entire field" (interview with CEO, NYSCF), geared to ensure the streamlined circulation of iPSC research findings among academic and, especially, commercial constituencies (Lowenthal et al. 2012; see chapter 2).

By means of this process of capacity–building, NYSCF sought to position itself as a *translational hub* (Fishburn 2012), situated at the core of a vast network of academic and clinical centers, advocacy organizations, biotech and pharmaceutical companies. By establishing internally the cognitive and material infrastructure purportedly needed to connect these different kinds of organizations, each focused on a specific aspect of stem cell research, it thus aggressively pursued the final aim of facilitating the uptake of academic research by clinical, biotech and pharmaceutical organizations.


**Figure 4: NYSCF as translational incubator at the core of an integrated discovery nexus.**

### 4.3.3 A new model of governance: venture philanthropy.

We thus see at work, in NYSCF translational pursuit, a twofold reconfiguration of stem cell research: a *spatial* insulation from political hindrances coupled to a *temporal* acceleration over traditional modes of scientific scrutiny. Essential to this reconfiguration was the development of an innovative regime of governance, which represents a distinctive trait of NYSCF's endeavor in the stem cell field.

For one thing, insulation from the federal political environment was achieved through the almost exclusive reliance on private funding. A skilled, well–connected fundraiser, NYSCF's CEO was able to mobilize a large wealth of resources, provided by patient advocacy and charitable foundations – such as the Helmsley trust and the Michael J. Fox Foundation for Parkinson's Research – as well as affluent philanthropists from the New York City's financial élite. The latter set of people, in particular, played a key role for the scale up of NYSCF's operations. If the first donation received by the organization amounted to 100,000 USD, provided by a fellow member of a distinguished urban research and advocacy organization, the Regional Plan Association, in whose board Susan Solomon has served for many years (interview with chief of staff, NYSCF), the involvement of major hedge fund executives greatly augmented the flow of resources available to NYSCF. By tapping into the wealth of Wall Street billionaires such as Julian Robertson (manager of the Tiger fund) or Stanley Druckenmiller (former manager of George Soros' renowned Quantum fund) – who became prominent funders of the organization – NYSCF was able to both set up enticing funding schemes for investigators all over the US, and establish its own high–tech, high–cost research infrastructure.

Moreover, other than with respect to its funding strategy, NYSCF's 'New York City dimension' – as one of my interviewees defined the close–knit link that ties NYSCF to its geographical location at the epicenter of the world's financial industry (field notes 2015) – is brought to bear on the governance structure being implemented by the leadership of the

organization. Backed by private philanthropists' money, NYSCF adopted – unique in the whole stem cell field worldwide – a *venture philanthropy* regime of governance, one that was meant to greatly enhance the translational capability of the organization.

Articulating a new model for philanthropic funding, venture philanthropy rose to prominence in the mid–1990s[10], around the time of the dot–com boom, borrowing concepts and practices from venture capital funding (which was widely used in the 'new economy' to start up businesses and support their capacity–building process), and deploying them for innovation-oriented organizations in the non-profit sector (Grossman et al. 2013). Drawing moral legitimacy and resonance by appealing to pro-business values and a pro–market ideology that fits with an "MBA-type of thinking" typical of potential donors (Moody 2008), venture philanthropy also resonated with a pragmatist sensibility that values things "because they work" (Dart 2004) - all pervasive elements within the American civic epistemology (Jasanoff 2005) and socio-political culture. As sociologist Michael P. Moody (2008) observes, "it appears there was this sort of natural fit between venture philanthropy and the existing venture capitalist-oriented ways of thinking and acting that prevailed among many of the newly wealthy individuals at this time, many of whom were either the beneficiaries of venture capital funding or the venture capitalists themselves."

Having thus rapidly developed into a "'new' organizational field" and "'new' professional culture" (Moody 2008), the venture philanthropy model has aimed to mark a departure from traditional models of philanthropic giving, through the adoption of an *outcome-driven, evidence-based approach*. In particular, by employing methods derived from venture capital, such as due diligence and risk and performance management (Grossman et al. 2013), venture philanthropy–backed organizations are meant to achieve a

[10] More precisely, venture philanthropy was first introduced as a concept, to articulate a new model for philanthropic funding, in an influential 1997 Harvard Business Review article that, however, did not even contain such wording (Letts et al. 1997).

twofold objective: first, to defy the inefficiencies and "the internal bureaucracy typical of large organizations" (interview with CEO, NYSCF); second, to implement, quickly and effectively, the purpose for which philanthropic money is allocated[11]. As explained by the chief of staff of the organization,

> *Our model of governance is a venture philanthropy, accelerated model, and this is what sets us apart from other research institutions. We don't have to rely on federal funding, and we are able to take fast decisions - much faster than academic organizations with large bureaucracies. We are quick to identify where investments should be made, and then embark in that very quickly. And this is key to bring us faster to new treatments.*
>
> Interview with Chief of staff, NYSCF

Drawing from this template, NYSCF designed its governance structure accordingly. For one thing, building on the venture capital expertise of its CEO, it set out to maximize the effectiveness of its management strategies, and adopted a marked outcome–driven approach. The CEO claimed that:

> *I try to keep things as flat as I can, organizationally […] First of all, it's just facts. 90% of our money is used for direct programs, 10% to keep the lights on. That is pretty extraordinary… And people who are more in the professional philanthropy business, have said that they feel NYSCF is giving them the best return on any philanthropic investment that they have made. So, we are very results oriented…*

[11] Grossman and colleagues (2013) explain: "In 2011, non-religious philanthropy in the U.S. totaled $202.54 billion. Trillions of additional dollars have been given to nonprofit organizations over past decades. Yet philanthropists are increasingly frustrated that their goals of improving public education, reducing homelessness, or increasing job readiness still seem elusive. Despite conventional wisdom, the dearth of philanthropic results may be less a function of the total amount spent and more a product of the way money is traditionally given to nonprofit organizations. For the most part, philanthropy is distributed for specific programs, for relatively short periods of time, and with little accountability for results. Even when a nonprofit can prove its effectiveness, donors rarely provide enough growth capital to enable organizations to impact a societal problem at scale. […] Venture philanthropy takes a different approach."

Second, and most relevantly, it bestowed agenda setting prerogatives to a composite set of philanthropists and patient advocates – thus empowering them as the privileged constituency the organization is meant to serve – and set accordingly its own criteria of accountability. More to the point, in charge of maintaining fiduciary responsibility for the organization is a varied board of directors which comprises patient advocates, top Wall Street executives, leading clinicians and scientists and even a Pulitzer laureate for distinguished architecture criticism (i.e. Susan Solomon's own husband) – "people who care about the issue and are supporters of the organization, who Susan knew, who are well established and respected, and could bring responsible governance and different trains of thoughts to the organization" (interview with chief of staff, NYSCF). Furthermore, the board of directors is where CEO Susan Solomon, who is "in charge of everything" (interview with chief of staff, NYSCF) reports and is held accountable; it acts as *trait–d'union* between the donors (some of whom sit on NYSCF's board) and the organization itself; and also, by ensuring that primary responsibility for research oversight is retained within the organization – something that, in spite of potential criticism, is hailed as "critical" by NYSCF's CEO (interview with CEO, NYSCF) – it is also meant to construct, and preserve, the "integrity" of "NYSCF's own view" on stem cell research (interview with CEO, NYSCF).

The predominant role played by philanthropists and patient advocates within the organization also influenced NYSCF's ethical oversight strategy. The chair of NYSCF's SCRO committee notes in vivid words that:

> *The biggest difference of our SCRO committee is that the membership is spread out all across the country. Other SCRO committee have all local members. We are a sort of "virtual reality SCRO", we meet by teleconference. I think this is interesting if you think about deliberation: what happens if we have to deliberate on something controversial*

*and we don't meet face-to-face? The other difference is that NYSCF's SCRO committee is tilted a little bit more heavily towards community members. If you look at the eight of us, there are two scientists, bioethicist, one of the legal guys is also a patient advocate. So, roughly half of them are patient advocates, which is significantly more than e.g. the [other] SCRO committee, where we have one community member. […] Furthermore, I think people see the SCRO has being very friendly towards NYSCF, that's my impression. Everyone has got a very favorable view of the organization, that's why the volunteered to be part of SCRO.*

Interview with chair of SCRO committee, NYSCF

### 4.3.4 NYSCF as sociotechnical vanguard – Accelerating by disrupting.

In light of the above, drawing from the cultural repertoire (Lamont and Thevenot 2000) of American (venture) philanthropic innovation, in which pro-market and pragmatist attitudes converge (Dart 2004; Moody 2008), NYSCF was thus able to carve for itself the role of what Hilgartner (2015) designates as a *sociotechnical vanguard*. Precisely as a private capital-backed organization adopting a venture philanthropy-based governance model, NYSCF could frame its endeavor as that of *a visionary avant-garde*, predicated on the virtue of unleashed scientific *knowledge* matched to equally unleashed *means* to translate it.

Faithful to venture philanthropists' quest for innovative, disruptive advancements leading to "pattern-breaking social change" (Childress 2008), this convergent unleashing of knowledge and means was explicitly framed as the core of NYSCF's mission as a "game changer" promoting *disruptive innovation* in the stem cell field (Bower and Christensen 1995; Christensen 1997)[12]. As most eloquently attested by the following interview excerpt,

[12] Defined by influential Harvard Business School scholar Clayton Christensen as introducing "a very different package of attributes from the one mainstream customers historically value", and even performing "far worse along one or two dimensions that are particularly important to those

what NYSCF's *vanguard vision* (Hilgartner 2015) typically mobilizes is the pioneering role of the organization in driving a wave of change that is contrasted with a gloomy scenario of unfulfilled translational promises should a "business as usual" approach happen to prevail:

> *The more I looked into the process of medical research, and what it could take to get the new field [of stem cell research] started, the more I felt I could make a contribution, as I have a background as a "change agent", I guess you could call it. I'm one of those people who could, I felt, also marshal others, who could look into new fields and look into the future, and see things that are not real today but can be real tomorrow, and this is not something that everyone can do…*
>
> *And then, looking around, and realizing that if we left it as business as usual... the analogy that I like to use is [with hurricane] Katrina, where everyone assumed that everybody else was bringing the ice, and nobody brought the ice to all these poor people stuck in the Dome. And I know that a lot of these people assumes that the system is taking care of things, but either it's not, or not in a reasonable amount of time...*
>
> Interview with CEO, NYSCF

Consistent with this disruptive ambition, "bringing the ice" to the stem cell field took the form of a specific organizational gearshift revolving around the implementation of a marked *risk-prone approach to stem cell science* that spanned from the *financial* resources all the way to the *epistemic* depth of technologies and machineries.

As to the former, against the backdrop of risk-adverse funding agencies (Ledford 2012), increasing decommissioning of the pharmaceutical industry from early phase drug discovery (Bartek 2014) along with its reluctance to invest in a largely immature stem cell

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customers" (Bower and Christensen 1995), disruptive technologies are those that "typically enable new markets to emerge" by "redefining established trajectories of product performance improvement" (Christensen 1997), that is, in other words, by *defying*, rather than *meeting*, the demands and expectations of the customer base.

field (see chapter 2), NYSCF's strategy was to target financially "risk-taking, early stage work that is essential for translation" (interview with CEO, NYSCF), so as to de-risk downstream, industrial research and thereby accelerate commercial development. For instance, since the establishment of its robotic platform in 2013 (see below), a major aim of the organization has been to pursue the scale up of iPSC research, so as to establish the proof–of–principle that academic research findings obtained on a small numbers of cell lines could in fact be robustly replicated on a large number of samples within an industry–compatible infrastructure. As NYSCF's director of scientific programs explained in that regard:

> *When people put commercial dollar into something, they trust that the results they are going to get are what they want...and that it's a good investment. And right now the stem cell field is* not *a good investment. That's why we are a non-profit company. We know how to make it a good investment, but we just need to get over that hurdle so to get people trust it. And once we're there, we're going to have personalized medicine, cheaper clinical trials, we're really going to change the face of the health care system..."*
>
> Interview with director of scientific programs, NYSCF

Not only meant to *accelerate* the commercialization of research findings, NYSCF's engagement with high–risk research was also intended to sustain the *completion* of research projects filled with uncertainty – also by devising accordingly its IP strategy. Whereas venture capital–backed start–up companies are in fact typically oriented towards an *early* out–licensing of their findings to major pharmaceutical corporations for further product development (Mazzucato 2013), NYSCF set out to retain the long–term intellectual property of its research findings, so as to make sure that the out–licensing doesn't occur *too early* into a compound's translational trajectory, that which could entail

its death sentence. “We are not in the fashion business, we are in the patient business”, argued the CEO of NYSCF. Before explaining further that:

> *at the typical, major stem cell program in the university the work is really not translational, in the sense that it is done at a small scale, and the incentives are either aligned for tenure and publication, and getting more grants, or to commercialize, to license patents to drug companies that have their own challenges – and you are then at the mercy of the fashion business, whether you are going to move ahead or not, because one minute they want to be in the pain business, the next decide no, no, no, they want to be in the Alzheimer business. There are no incentives, you are not rewarded for ongoing risk-taking…*
>
> Interview with CEO, NYSCF

Moreover, consistent with its 'safe haven lab' approach, NYSCF has constantly engaged in ethically or politically controversial kinds of research. For instance, owing to its insulation from the federal political environment, as well as to its location in New York State, which allows compensation to women for oocytes provision, NYSCF has for many years spearheaded research on SCNT (see e.g. Chan et al. 2012; Yamada et al. 2014). As the chair of NYSCF SCRO explains:

> *They definitely have as a central part of their mission to fund research that maybe wouldn't be easily fundable through other sources. SCNT is a proper example for that. I am sure they view themselves as facilitating research otherwise difficult for political reasons or pressure... With the ethically controversial SCNT, for example, they are much more willing to facilitate that kind of research: it's part of their self-identity, their are the ones who really try to push forward every aspect of research (and SCNT is just an aspect of this).*
>
> Interview with chair of SCRO Committee, NYSCF

Finally, as far as the epistemic dimension of risk-taking is concerned, it took the form of "something so new as to be absolutely unique" (interview with investigator, NYSCF): the *Global Stem Cell Array* (henceforth: GSCA).

### 4.3.5 Epistemic reconfigurations. "Something so new as to be absolutely unique".

As shown by a large body of STS scholarship (see, e.g. Fujimura 1987; Scott 1988; Bowker and Starr 1999; Webster and Eriksson 2008; Timmermans and Almeling 2009; Nowotny and Testa 2011; Busch 2013), standardization practices and technologies are potent vehicles through which normative rationalities and visions acquire material currency.

NYSCF's commitment to act as stem cell translation catalyst was epitomized in the implementation of the first fully automated, robotic system for the parallel derivation of hundreds of iPSC lines. Taking four years for completion, at an overall cost of over $35 million, the GSCA (field notes 2014; Paull et al. 2015) became fully functional in 2015 to automate the derivation, culture and expansion of iPSC lines, as well as their differentiation into various lineages from all three embryonic germ layers, such as cardiomyocytes, midbrain-type dopaminergic neurons, hepatocytes, metanephric mesenchyme, and oligodendrocytes (Paull et al. 2015).

In a matrioska-like arrangement, the GSCA represents a "central iPSC derivation hub" that enables "the seamless connection" (*ibid.*) between clinical donors, end user scientists as well as pharmaceutical companies, thus materializing into scientific practice NYSCF's organizational configuration as a *translational hub*. Furthermore, as a capital-intensive effort aimed at bringing technological closure to the standardization of human stem cell pluripotency, a field whose epistemology is still very much in flux, the GSCA plastically instantiates NYSCF's *risk-prone* approach to stem cell research. As recalled by a NYSCF Investigator during a visit to the facility that I conducted in April 2014:

*The idea was, what could we do that is so large that nobody else would be able to realize, that the NIH won't finance…? And this is how they came up with this project, which is such a high-risk project that we still don't know whether it is going to be rewarding. I believe the idea was precisely to do something so new as to be absolutely unique.*

Interview with Investigator, NYSCF

More specifically, by aiming at reducing biological and technical variability inherent to manual iPSC derivation and differentiation (Paull et al. 2015) - as well as greatly increasing their 'throughput' and scale -, the GSCA is geared to accomplish a threefold translational objective. First, it "enable[s] the application of iPSCs to population-scale biomedical problems" (Paull et al. 2015), providing "a platform for large-scale *in vitro* studies" (*ibid.*) such as the study of complex genetic diseases with modest effect size that require large cohorts of samples to probe the genetic contribution to phenotypic variation, thus corroborating the notion of iPSC-based functional annotation of human genomes pioneered in the work by Adamo, Atashpaz, Germain and colleagues (2015). Second, it underpins the creation of an *iPSC repository* (nyscf.org/repository), set up in collaboration with the Harvard Clinical and Translational Science Center (Harvard Catalyst), aimed at enhancing access by the scientific community to a vast panel of well-characterized iPSC lines from diverse populations of diseased patients.

Third – and crucially – the GSCA is meant to facilitate the pharmaceutical development of iPSC-based technologies, in a twofold way. On the one hand, it represents an infrastructure well suited for high–throughput screenings of new compounds on iPSCs and iPSC–derived cells (see chapter 2). The novelty of the system, however, has been met with lukewarm reception from pharmaceutical companies. The head of the stem cell program at a leading pharmaceutical company explained for instance in May 2014 that:

*We were in contact with NYSCF, I visited them one year ago, I mean... I am impressed by what they are doing, but currently it does not fulfill the needs of [COMPANY]. […] You know, there are huge costs, and finally for us, the quality of the cells is really crucial, and I think the science has to progress a little bit. We still clean the cells manually, we change the media every day, and we check the quality every couple of days, if there are cells that are starting differentiating we remove them manually. In a 96–wells plate you can't! If they loose a colony, they loose it and use another one... Maybe this is the way forward... For our logistic, the way we are doing, with a lot of manual steps, makes currently more sense... Only the media for iPSC, this will develop so fast, that in two or three years it becomes much easier, and then also automation really becomes feasible.*

Interview with head of stem cell program at multinational pharmaceutical company

On the other hand, and in a much shorter timeframe, the GSCA is geared to establishing the proof-of-principle that discoveries made in academic laboratories, on a small number of iPSC lines, can be replicated, scaled up, and validated in a robust manner across a large number of cell lines. It thus provides the level of standardization required by large application-driven organizations so as to ensure, accordingly, the attainment of *industry–compatible standards*. As explained by NYSCF's director of scientific programs:

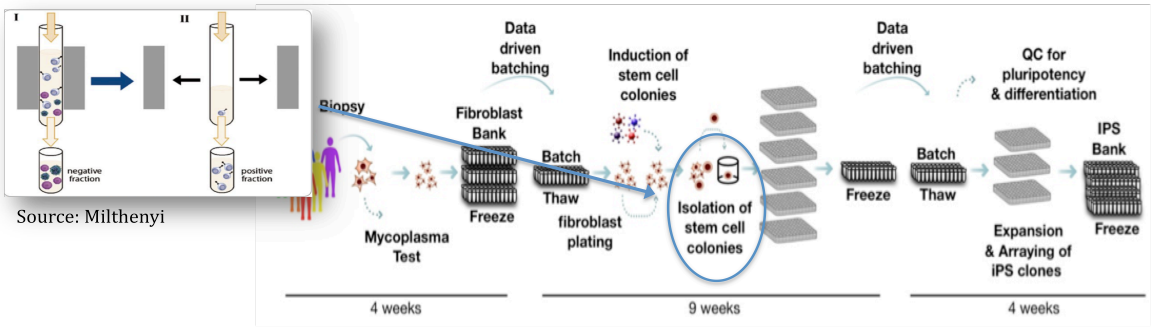
*If you have projects that you think are relevant to identify a drug or something interesting about the disease and its biology, how do you get other people across taking it for real? And having a group validating it, scaling-up across a large number of samples and cell lines is really a critical component. Pharmaceutical companies are not trusting academic laboratories, but I think the partnership between us and the labs has got a lot of interest [from pharmaceutical companies]. When someone says they generate a kidney cell, can you really generate a kidney cell, does that protocol works across different samples, outside your lab?*

### 4.3.6 Reconfiguring the epistemology of iPSCs.

The CEO of the organization recalled the decision to pursue the road of iPSC automation in the following terms – which point to the aim of *transferring* human skills to robotic machines:

> *We looked at how stem cells were made and said: "look, this is terribly inefficient, it's super-slow, you can only make a few at a time, and you are doing by hand, and you are tying up really expensive talent seven days a week basically feeding pets! So, let's see if we can teach robots to do this…*
>
> Interview with CEO, NYSCF

However - as it is often the case in biomedicine (for instance, see Keating et al. 1999; Keating and Cambrosio 2003) -, the implementation of the robotic system did not consist in the replacement of human with non-human agency in order to (re)produce the same output. Rather, it triggered the development of a new protocol of iPSC derivation and differentiation that thoroughly reconfigures the ontological materiality of iPSC lines (Paull et al. 2015). In fact, automated reprogramming reconceptualizes the standard, "most under-appreciated yet most important control instrument for pluripotent quality assessment" (Muller et al. 2012), namely the visual inspection and manual selection of "good looking" (i.e. fully reprogrammed) from "ugly looking" (i.e. partially reprogrammed) "colonies" of cells (see chapter 2). Optimized for the robotic practice *and* epistemology, the new protocol entails the disruption of the colony of cells into single cells, that are then individually sorted for pluripotency markers, and finally pooled together so as to have a mixed (polyclonal) population of cells purportedly displaying "less line-to-line variation than either manually produced lines or lines produced through automation followed by single-colony subcloning" (Paull et al. 2015).




Source: Milthenyi

Source: NYSCF

**Figure 11: iPSC colonies *vs* single cells – workflow of the GSCA.**

Interestingly, the reason for adopting the new protocol was twofold, and it was dictated both by epistemic reasons (i.e., it introduces less variation) and as a consequence of the need to shift "from systems that are still returning knowledge through their instability and need for skill to reliable, highly quality-controlled processes" (Fisher 2012). The decision to opt for the cell sorting technique, rather than the standard colony picking procedure, was explained by the engineer in charge of devising the system in the following terms:

> *If you want to do the picking, you need to localize the good colony in the well, where it is. And how do you do this in an automated fashion? Manually, if you look under the microscope you can pick and transfer colonies by hand; with automation how do you control the variation about where colonies could be popping up? It's possible to do that, you can do staining, imaging, etc., but it's more complicated, more time-consuming, and would be difficult to make that amenable to a large batch-factory type process. Whereas, if you remove everything from the well, and do cell sorting, etc, it's more amenable to a large-scale process.*
>
> Interview with senior system architect, NYSCF

Thus, through the automation of iPSC derivation, NYSCF's self-proclaimed disruptive approach gets translated into the very materiality of its own experimental practices. Not only does NYSCF aim at disrupting - *figuratively* - established scientific practices and

markets; in order to achieve this aim it takes the road of disrupting - *literally* – the epistemic and thus far nearly sacred unit of iPSC science, one that owed its value to the very care with which it was managed as a biological whole: the colony of pluripotent cells.

In parallel, the translation-driven automation of iPSC derivation entails a further crucial reconfiguration, propelling the transformation of the GSCA-based *experimental system* into a *system of production*, "laden with connotations such as directivity, efficiency, quantitation of output" (Rheinberger 1997). Whereas scientific experimentation strives to engender new, unexpected events, the *epistemic things* that "give unknown answers to questions that experimenters themselves are not yet able clearly to ask" (Rheinberger 1997), the GSCA turns iPSCs into *technical objects* (*ibid.*), devoid by intention of any epistemic uncertainty, and hence scientific interest, of their own. Indeed, while indeed the stem cell field still struggles creatively with the notion of pluripotency as a yet-to-be stabilized object of inquiry (see, e.g. Kalmar *et al.* 2009; Nichols and Smith 2009; Gafni *et al.* 2013; Obokata et al. 2014), automation requires that such uncertainty be tamed, the epistemic currency of such questions be devalued, and the search for "the better standard" come to a closure.

As such, automation represents not only a key moment in the standardization trajectory of iPSCs, but also the moment in which "*they almost leave the lab*" (interview with iPSC scientist) and become akin to a *commodity* (Marx and Engels 1970): something that, in virtue of its highly standardized nature, severs the ties that bounds it to the (laboratory) context of its production, can circulate across different experimental settings, while being enrolled, as a consequence, in circuits of high return, be it experimental, curative or bioeconomic. As a prominent iPSC scientist put it, capturing by means of analogy the profound reconfiguration underwent by iPSCs through automation:

> *The analogy which you have to make is with the Louis Vuitton hand bag: [...] it is handsome, hand-designed, there are only some that are made per year, etc,*

*whereas if you go to your regular department store, let's say Walmart, you'll have something that is mass-produced, there are millions of them, and it's a completely different thing.*

Interview with iPSC Scientist

### 4.3.7 Conclusions.

In this chapter, I have outlined the most significant junctures in the chain of events leading to the current policy configuration of the field of stem cell research, before moving to expound how they have been brought to bear on the configuration of a leading iPSC research institution in the US, the New York Stem Cell Foundation.

NYSCF's endeavor represents a unique case in the field of stem cell research, and in many respects a fascinating one. Propelled by the means of the sector with the highest return on capital in the world, the financial industry, it set out to programmatically accomplish a disruptive mode of scientific enquiry, supported by an equally innovative model of scientific governance, that of venture philanthropy. As its vanguard vision (Hilgartner 2015) finds material currency in the implementation of the first fully automated robotic system for iPSC derivation, expansion, and differentiation – a feat considered "so high risk that it is still not known if it is going to be rewarding" – it symmetrically empowers a small set of exceedingly wealthy and tech–savvy stakeholders, and frames them as those who are better positioned to advance translational stem cell science in the search of cures for the 21st Century.

I will reflect more in depth on these aspects, and on what they do entail, at the end of the present dissertation. Before I do so, I travel the short distance that separates New York City from Cambridge and Boston, MA, to analyze, in the next chapter, the uptake of iPSC research in a bastion of academic research, Harvard University.

# Chapter 5. The Harvard Stem Cell Institute

The genealogy of the Harvard Stem Cell Institute – with more than a thousand affiliated researchers, the largest stem cell research organization in the world – owes in critical ways to its institutional affiliation at the core of America's oldest and more prestigious academic institution, Harvard University. HSCI was established in 2004, out of privately-raised funds, as a "networked organization" (field notes 2015) connecting several institutions, schools and affiliated hospitals within Harvard, with the goal of leveraging these resources to advance stem cell science and its clinical application. In particular, internal academic as well as broader political motives synergistically propelled the creation of the new institute.

For one thing, since the beginning of the new century, and the appointment of economist Larry Summers – a former chief economist of the World Bank and Secretary of the Treasury in the Clinton administration – as its 27th President, Harvard University has decisively pursued a path of heavy investment in the biosciences, with stem cells figuring prominently among them. "I am convinced that the next Silicon Valley… will happen in the biomedical area, will happen in the technology and in the products that relate to extending and improving the quality of human life", declared Harvard president Larry Summer in November 2001, a month into its tenure (Schlesinger 2005).

Attesting to the significance of Harvard's endeavor in the area, largely fueled by its massive endowment, which in 2004 totaled 22 billion USD, were initiatives such as the creation of the Broad Institute (a 200 million USD joint venture with MIT to find clinical applications of the human genome), or the completion of the 260 million USD New Research Building at the Medical School (Schlesinger 2005). Most notably, contributing to the sense of transformation –made manifest through visible changes in the university's

urban landscape – was the projected creation of a new scientific hub resulting from the expansion of Harvard's Allston campus, located south of the Charles river, and just half a mile away from Harvard's main campus in Cambridge, MA – an area already home to the university's Business School and its main sporting facilities. At the core of the new projected Allston Science Complex – meant for completion in 2010 (Lok 2007), before plans were scuppered due to the massive losses incurred by Harvard's endowment fund following the 2007 financial crisis (Groopman 2009), and before they have been resumed for good in Spring 2014 – was to be the newly established Harvard Stem Cell Institute. There, researchers and professors from the faculty of Arts and Sciences, the Medical school, and the School of Public Health would have been "working days and nights unraveling the mysteries of the human cell" (Schlesinger 2005). Likewise, members of the Law School, the Business School, the Kennedy School of Government, and the Divinity School would have gathered so as to explore the ethical, business and social dimension of the new technology.

Aside from Harvard's long–term goal of enhancing its already world–renown capability and expertise in the life sciences, matters of current political affairs were at play in propelling the creation of the institute. HSCI set indeed out, in the words of then Harvard's President Summers, to circumvent and compensate for the Bush Administration's "deeply misguided policy" on stem cells, which amounted to the "abdication of national responsibility" in the area (Harvard's Office of the President 2004). Addressing a packed audience at the institute's inaugural symposium in the Charles Hotel in Cambridge, on April 24, 2004, Democrat Summers revealed his well–honed "sense of the inherent powers of the Harvard presidency", by "dar[ing] oppose", in the quest for advances in the field, the university itself and the Republican federal government (Schlesinger 2005):

*That the federal government has withdrawn from funding so central a scientific area imposes, I believe, a great ethical obligation on the very, very small numbers of*

*institutions within our country that have the capacity to fill that gap […] Filling in a gap like this is the highest and best purpose for a university like ours* (Harvard's Office of the President 2004).

Far from being a lonely, albeit powerful, voice, Summers' words resonated with a widespread feeling within the Harvard community. As vehemently argued by prominent HSCI scientist George Daley, who was previously involved in planning the new initiative, no one was in doubt that "Harvard has the resources, Harvard has the breadth, and, frankly, Harvard has the responsibility to take up the slack that the government is leaving" (Vries 2004).

In his speech, Summers further added rhetorical momentum to his claims by "fearlessly amending" (Schlesinger 2005) Harvard's famed rubric ("*veritas*"): "we value truth for its own sake, but we also value truth because understanding can make a profound difference in this world and a profound difference to millions of people's lives" (Harvard's Office of the President 2004).

Highlighting the curative promise entailed by the new technology, he also appealed to his own personal biography, and his healing from Hodgkin's disease, a disturbance in the cells of the lymphatic system, which almost killed him as a young man, to justify sustained investment in a field whose fungible rewards lie intangibly far into the future. "Some 20 years ago I spent no small amount of time in one of Harvard's great teaching hospitals, being treated, with the ultimate outcome in some doubt for a time. My treatment worked out very well", he explained at the symposium. And continued: "And when that course of treatment ended, I asked a question. I asked: At what point in the development of science, what point in the development of the relevant research, had the discoveries been made that had made possible my treatment? The answer was, about 10 or 15 years before I was treated… And I thought to myself, wasn't I fortunate that that research program had been pursued as aggressively and as quickly as it had" (Harvard's Office of the President 2004).

Backed by Harvard's most powerful figures, and driven by the aim of sustaining the promising, albeit hindered, hESC research, in Spring 2004, soon after Summers' inaugural remarks, HSCI started its operations. In particular, making what, at the time, was a major statement of intent against the policy of the Bush Administration, it started deriving, and distributing to the broad scientific community worldwide, a large number of hESC lines, some of which have become among the most used in the field (Scott et al. 2009). The co–director of the institute noted that:

> *the first objectives were to create and distribute embryonic stem cells for researchers to try new things. That took a year or so and within the first year, I think, Harvard literally distributed thousands of cell lines for free to the world over. And I think this was the right thing to do, and I would do it again, because I don't think we're smart enough to know what people should do with this reagent, with this tool, and I like the idea that people anywhere could do this kind of work. I make a joke of it and say: my grandparents came from Bugnara, which is far in the East coast of Italy, in Abruzzi. There might be a researcher there who wants to do something, and I am not smart enough to tell them what to do, but they should be able to do whatever they want…*
>
> Interview with co–director, HSCI

### 5.1.1 "*If you stand alone it's much harder than if you stand together*". A citadel of science against the President siege on stem cell research.

Whereas NYSCF's endeavor owed in many respects to its geographical proximity to New York City's financial industry, HSCI significantly leveraged on its location at the heart of a world-renowned biotech hub in the Boston area, whose concentration of resources and expertise in the life sciences led former Harvard's president Summers to a comparison to fifteenth–century Florence in the arts (Schlesinger 2005). Hence – to resort again to Summers' arguably far–fetched metaphor – similarly to the affirmation of

humanism in the Italian Renaissance, which greatly owed to the gathering and exchanges of a broad array of intellectuals in city–states politically autonomous towards the imperial and religious powers (Garin 1969), Harvard's stem cell pursuit draw strength from the establishment of dense connections among the Boston area's many research institutions. As explained by the co-director of the institute:

> *We felt – I think not unreasonably - that if we bended together all of the institutions in Boston that would make... you know, if you stand alone it's much harder than if you stand together. I think that turned out to be true, all the hospitals and universities joined together, which gave them a lot of strength and a shield or protection against some of what I would consider to be the political non-sense and the legitimate religious questions.*
>
> Interview with co-director, HSCI

**Figure 12. Harvard–affiliated institutions: 1a Harvard Medical School, 1b Boston Children's Hospital (photo: LM)**

The words of HSCI's co–director underscore a key point concerning the guiding principle underpinning the establishment of the new institute: the quest for protecting the *autonomy* of Harvard's scientific community from what are referred to as "illogical political interferences" (field notes 2014).

In order to achieve this aim, and set the new organization up and running, further steps were needed other than recruiting and assembling a broad network of researchers, in competition with other prominent research centers such as Rudi Jaenisch's Whitehead

Institute at MIT, where many of HSCI's newly acquired and soon–to–be–famed stem cell scientists headed from (Matlack 2009).

The first objective was the creation of a new independent 'institute' within Harvard, so as to benefit from the university's wealth of resources and expertise, while also maintaining a formal degree of independence from its (varied and complex) internal funding mechanisms, bureaucratic structures and academic politics – the latter centered on the powerful figures of the deans in charge of each school (Golub 2007; field notes 2014). Conceived as a "virtual company inside Harvard" (field notes 2014), HSCI's institutional configuration as an independent entity gave it leeway in setting its own research agenda, raising its own funds, while also reaching out more easily to external companies. As recalled by the co–director of the institute, and a former HSCI investigator:

> *The first steps were to get permission from university to start a group of people who would work together, and create an institute. And an institute is not a common word within the university, it's not a department. A department has the ability to make faculty appointments, but we didn't ask for that. We wanted to have the ability to raise funds, hold meetings and organize research.*
>
> Interview with co–director, HSCI

> *HSCI is able to do things because it is not a department. It has a discretionary nature over its budget, it can build partnerships with the private sector, in a much more seamless way…*
>
> Interview with former HSCI investigator

Accordingly, a second fundamental step to preserve the autonomy of the institute was to provide it with an adequate level of funding. Thus, aside from the financing coming from grants awarded to investigators by outside agencies, which amounts to around 80% of the available resources, HSCI was able to set up a yearly pool of around $20 million, stemming primarily from philanthropic sources (field notes 2014). Interestingly, whereas

NYSCF's financing owes primarily to its outreach in the financial world, HSCI significantly leverages on Harvard's name recognition and its broad network of alumni:

> *The university's development office has a lot of connections with our alumni. When these development officers meet with their philanthropists, philanthropists ask them what's going on at Harvard and many of them will say one of the most exciting things is HSCI.*
>
> Interview with co–director, HSCI

Finally, a third key objective pursued by the nascent institute concerned the establishment of an appropriate steering and governance structure, one that could protect its scientific autonomy, while also enhancing the effective collaboration among researchers. To this end, HSCI resorted to the appointment of an executive committee, of around ten members, entirely composed of scientists and clinicians working in various Harvard departments and affiliated hospitals, in charge of the institute's budget, as well as of the scientific review of its projects. As explained by the co–director of the institute:

> *[Members of the committee] have different scientific expertise and come from different hospitals in the system – and it's that group that decides funding, and reviews the projects. That group decides everything. So even though I am a director, I do not make many decisions on my own.*
>
> Interview with co–director, HSCI

Furthermore, as a mean to increase the institute's management capacity, and expand its outreach towards biotech and pharmaceutical companies, in 2006 HSCI appointed an Executive Director, a former Harvard MBA with extensive experience in the private sector, one that could add robust administrative expertise to the leadership of the institute. In particular, among the "trickier issues" that needed to be dealt with appropriately were the negotiation of intellectual property rights, how to coordinate investments in ongoing stem cell research in the various institutions, and how to jointly market and profit from the

discoveries (Golub 2007). Reflecting on his own appointment, the executive director explained:

> *Think about HSCI as a virtual company working like a venture capital group. There are multiple aspects to the business of HSCI: raising money, deciding where to put it, communicating about it to our donors, manage the projects, work with faculty to sponsor research with disease foundations and companies, in some cases helping license work to company, connect people with venture capital (when they want to launch start-up)…*
>
> Interview with executive director, HSCI

As a whole, these measures were geared to enhance the scientific autonomy of the institute, and facilitate the seamless integrations of its different research components. Put in different terms, the establishment of HSCI's governance structure was driven by the attempt to resurrect, reproduce, and attune to the 21st Century the conceptual template of an ideal 'Republic of Science' (Polanyi 1962). In light of the perceived "Bush siege" on stem cell research, the response of the Harvard scientific community was to re-enact and fortify a self-governing 'citadel of science', with an executive committee representing the Harvard schools and teaching hospitals in charge of the steering and agenda-setting prerogatives, so as to ensure that the process of knowledge-production abides by science's inner professional standards and systems of incentives, and scientists are empowered to carry their own independent, self-coordinated initiatives, free from interference from the political authority (Polanyi 1962).

### 5.1.2 "The first enterprise at Harvard that captured the whole of Harvard".

Other than supporting hindered lines of research such as hESC research, as its underlying "primary goal" HSCI was meant to accomplish the distinctively translational task of advancing a "disease-focused science" (field notes 2015), harnessing basic

laboratory research in the biology of stem cells for the development of new clinical treatments. As observed by an HSCI scientist: "it is not enough to have the Nature paper. Ultimately, you want to impact the disease" (interview with HSCI scientist).

Differently from NYSCF's all-out translational thrust, however, a key objective of the institute is to "strike the right balance between basic science and converting that science to clinical applications" (field notes 2015). A right balance that, owing to expectations related to Harvard's illustrious history as a source of cutting-edge discoveries, as well as to the fact that "the Harvard system, because of its name and its 'culture', is probably more conservative clinically that lot of other places" (interview with Executive director, HSCI), involves, alongside explicitly translational programs, preliminary significant investments in basic science:

> *For us, the focus on basic research is huge, most of our research focus is on basic science, on how to understand mechanisms and solve fundamental problems. There are other non-profit organizations that are much more focused on translation...*
>
> Interview with executive director, HSCI

More in detail, HSCI set out to implement funding schemes aimed at accomplishing three complementary objectives: to support, through targeted *seed grants*, early stage projects, oftentimes setting out unproven paths of research (“when you have a crazy idea in the bathtub – argues HSCI’s co–director – and you want to try it, you’ll never get a grant for that idea. So we use our philanthropic money, […] to use the seed grants to start new projects and to get projects going”); to establish a small number of *core facilities* comprising shared equipment and skilled personnel that no single laboratory could support on its own; and to advance several *disease projects* focused on elucidating the molecular etiology of, and developing treatments for, diseases in areas ranging from cancer to cardiovascular to central nervous system diseases.

To realize its translational vision, HSCI adopted an organizational strategy that could "tie together" research models of different types of institutions, ranging from academic departments to funding agencies and the commercial sector, thus leveraging on their respective strengths, while "bridging the gap, both financial and scientific, left by these groups" (field notes 2015). Most prominently, it aimed at developing an "interactive culture" among Harvard-affiliated researchers and institutions, one that could overcome the one lab "silo" approach that has been characteristic of traditional research arrangements in biology (see e.g. Knorr-Cetina 1999), and one that evolved to become "the first enterprise at Harvard that captured the whole of Harvard" (field notes 2015; interview with Director of HSCRB department, Harvard University). As a former HSCI affiliate, and now director of the department of Stem Cells and Regenerative Biology at Harvard, went on explaining:

> *The days of the gentleman-scientist working in the basement and coming up with great discoveries are gone. Now it's about large teams requiring the expertise of many people, especially if you want to move into the clinic... So, the notion of collaborative research is not new, but I think the types of questions that are left have really pushed us towards thinking in different ways and engage in highly collaborative research. That's why the institute was put in place.*
>
> Interview with director of HSCRB department, Harvard University

Differently from NYSCF's centralized model, HSCI was thus conceived on the basis of a *distributed innovation* model hinging on the interaction of heterogeneous actors holding complementary pieces of knowledge (Felt and Wynne 2007). For one thing, in devising its steering structure (see section 5.1.1), the leadership of the institute paid special attention to the creation of mechanisms that could promote synergies among the institute’s vast

number of researchers, who possess distinct disciplinary expertise and belong to different institutions. As explained by HSCI's co–director:

> *When you get a grant from the National Institute of Health it may be for three or five years; at the end of that time you either published a paper or not. We set up a different program where we had milestones and productivity. And while we may commit for three to five years, if you haven't made any progress in the first couple of years, then we say we are not funding you anymore. Frankly, this ended up selecting through a different kind of researcher. It selected through a researcher who was a little less concerned about getting all the credit for themselves, because they had to work on a team, a little less concerned about being able to make every decision on their own without any oversight. In general, I would say, selected through people who would like difficult projects, that individuals cannot solve by themselves. I think it's a fuzzy distinction but it's different from the way science is normally done.*
>
> Interview with co–director, HSCI

Furthermore, in establishing its experimental structures, the underlying vision was that the best way to advance the field was not – differently from NYSCF – to accrue agency within a centralized laboratory facility, but rather to empower (by providing the missing connections and funding) those research structures that were already in place within the broader Harvard community, so as to being able to draw on an already existent, but left idle, set of resources, skills and expertise. As noticed by HSCI's executive director and the director of the department of Stem Cell and Regenerative Biology:

> *What is peculiar about HSCI is that we are a virtual research organization, an administrative team. We are set up without our own labs and infrastructure, but as a way of taking the stem cell perspective across the different Harvard-affiliated institutions.*
>
> Interview with executive director, HSCI

*NYSCF not only does a fundraise (primarily within influential people in NYC, Susan has a good network of people who are very passionate about this field), but also has its own lab. HSCI does not have its own lab. I think this is a very interesting approach: they have their own internal lab. HSCI does not have its own research lab. It has the iPS Core Facility, but I don't think a lot of research, discoveries, is happening there. It's production of quality control, and facilitating research because of the ability to make and engineer these different cell lines…*

Interview with director of SCRB department, Harvard University

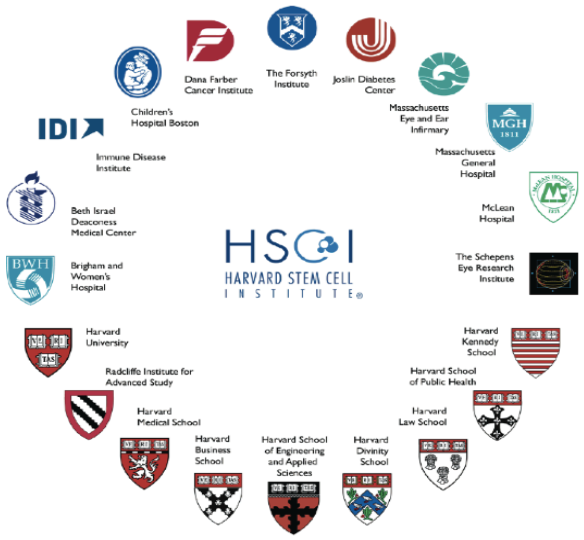



**Figure 13: HSCI as a virtual research organization (HSCI logo).**

### 5.1.3 Sustaining innovation in standardization practices: the iPS Core Facility.

Such configuration is consistent with, and shaped by, a *sustaining* (rather than disruptive) model of biomedical innovation (Bower and Christensen 1995; Christensen 1997), one that is geared to the development of experimental practices and technologies that, whether radical or incremental in character, are meant to be integrated within - rather than disrupt - established experimental technologies and practices. Other than in its

organizational structure, HSCI's sustaining innovation approach lends itself well to analytic scrutiny in the standardization practices designed and implemented within the only iPSC laboratory infrastructure it directly oversees, the iPS Core Facility.

Established in 2008, in order to have a small team of highly qualified iPSC scientists to master the rapidly evolving reprogramming technology, and adopting in 2011 a fee-for-service model, the iPS Core has been constructed within a *service-oriented framework*, as a way to "speed up the work in the Harvard network" by streamlining the provision of iPSCs and hence "take the burden off individual researchers" (interview with Head, iPS Core Facility) in performing routinary tasks (such as iPSC derivation, expansion, distribution) pertaining to the realm of "basic innovation" (Webster and Eriksson 2008). As explained to me by the head of the Core:

> *As reprogramming techniques became more standardized, people were interested in having these reprogrammed cells, but, first, why should every scientist learn how to do them on their own, spending unnecessary time reinventing the wheel in their own lab? – and second, some of the leading scientists we have here were not interested in making iPSCs, but rather in* using *them for their research.*
>
> Interview with Head of iPS Core Facility

**Figure 14. iPS Core Facility at HSCI (Photo: LM)**

More to the point, the core facility model (Ernst and Young 2012; Cambrosio et al. 2009) maintains some distinctive features that set it apart from NYSCF's standardization strategy.

In the first place, the Core aims at implementing a '*standardization on a customized basis*' approach, aimed at maintaining flexibility in the adoption of reprogramming methods and iPSC culture protocols. Rather than focusing on the scale-up of one kind of (emerging, and not yet stabilized) technology (something which could lead to a detrimental lock-in effect), the iPS Core aims at being able "to react quickly when new technologies come out", in order to meet the requirements of its customer base composed of (mostly) Harvard and non-Harvard scientists. The rapid inclusion of the new CRISPR/Cas9 gene editing technology among the services it provides is arguably the best testament to this. As the executive director of the institute said:

> *If the iPS Core were within a company, its job would be to say: 'how to make as many iPS cells, as cheaply, and efficiently, and effectively as possible...' The key would be repeatability, and scale, and costs. Because we are in the artisanal production mode - think about the small shoe factories in Northern Italy compared to the shoe factories in China -, the key is to say: 'look, we can make iPS with different techniques, that work best in different circumstances; we can knock a gene in/out, if you need that...' So it's standardization on a customized basis.*
>
> Interview with Executive Director, HSCI

Moreover, insofar as the routinary process of iPSC derivation is accompanied by the continuous tinkering with newly published protocols, in order to probe their potential adoption, iPSCs are maintained as *epistemic things* (Rheinberger 1997), whose epistemic currency as yet-to-be-stabilized research objects is still preserved intact. And finally, the Core maintains a risk-adverse approach with regard to the adoption of untested, unrobust

technologies. In that regard, rather than *creators* of innovation, core facilities can be more aptly described as "*consumers* of innovation" (interview with scientist, iPS Core Facility), lagging, and not leading, in the development of innovative technologies. Said the director of one Core Facility in New York City, capturing a widespread *modus operandi* among core facilities, and contrasting it to that of NYSCF:

> *I think that for me the strategy has been to linger at the back, and to let those at the bleeding edge let me know how it goes... instead NYSCF is on its own world in going out there and doing the risky stuff...*
>
> Interview with Core facility director

## 5.2 Notes from the field: the automation project.

Other than adopting a *fee–for–service model* for its reprogramming and gene editing services, the iPS Core also operates according to a *collaborative model*, as it engages in a wide spectrum of collaborations with different types of institutions. Whereas in the former case its agency is bound by the requirements of its customers, in the latter case the interaction takes the form of an interactive process, whereby iPS Core scientists, drawing from their expertise, actively contribute to shape the evolution of the project itself.

In particular, during the course of my fieldwork at Harvard in 2013 and 2014, the Core had been involved in three different collaborative projects. First, a NIH–sponsored, multi hub project aimed at deriving over 2700 iPSC lines from individuals involved at various stages in the Framingham Heart Study, one of the best characterized longitudinal epidemiological study for cardiovascular diseases and associated risk factors (Mahmood 2013). Second, a project sponsored by a major pharmaceutical corporation revolving around the molecular characterization of neurodegenerative conditions by means of iPSC–based models. Third, a NIH–sponsored project for the development of software–based automation of the process of iPSC colony selection.

The automation project (henceforth: AP), in particular, was highly revealing of the distinctive way in which the iPS Core operates, as well as the main differences that separates it from NYSCF's endeavor, for it can be fruitfully contrasted with NYSCF's implementation of its own automated system, the GSCA. In what follows, drawing from attendance to the five close door project meetings that took place during October 2013 and October 2014, as well as interviews conducted with the main actors involved, I thus provide a contextualization of the project and highlight some of its most significant features for the scope of this dissertation.

### 5.2.1 A SBIR–propelled project.

The AP started in 2012, following a three–year grant awarded by the NIH as part of its Small Business Innovation Research (SBIR) funding scheme.

Based on a National Science Foundation (NSF) pilot program, initiated during the Carter administration, the SBIR program was established in 1982, with the signing of the Small Business Innovation Development Act by President Reagan. The program requires government agencies with large research budgets, such as the NIH, to provide a fraction (originally 1.25 per cent) of their funding to support small enterprises (Mazzucato 2013), thus "encourag[ing] domestic small businesses to engage in Federal Research/Research and Development (R/RandD) that has the potential for commercialization" (sbir.gov). In particular, since its inception the program has aimed to foster interactions between academic research centers and small companies, in order to stimulate technological innovation and increase private-sector commercialization of innovations derived from federal research and development funding, while also encouraging "participation in innovation and entrepreneurship by socially and economically disadvantaged persons" (sbir.gov). As noted by Mazzucato, the SBIR program has represented an instrumental,

albeit low visible, part of the 'entrepreneurial strategy' of the US federal government, providing support to a vast number of high–tech start up firms:

> *The SBIR program fulfils a unique role in this new innovation system, because it serves as the first place many entrepreneurs involved in technological innovation go to for funding. The program, which provides more than $2 billion per year in direct support to high-tech firms, has fostered development of new enterprises, and has guided the commercialization of hundreds of new technologies from the laboratory to the market* (Mazzucato 2103).

In the specific case of the AP, the SBIR grant propelled the establishment of a collaboration between the iPS Core, a small bio–imaging company from the North–West of the US involved in software development for image–based decision solutions, and a major Japanese multinational corporation, which became involved in the project because of its product–development capacity (for the SBIR grant mandates, as a main requirement, the development of a commercializable product)[1].

Overall objective of the AP was the development of a software–based, bio–imaging system that could support automation of the process of pluripotency assessment and iPS colonies selection (see chapter 2). More to the point, by capturing real–time images of the cells being reprogrammed at specific intervals during the first three weeks of the reprogramming process, the bio–imaging system was geared to accomplish a twofold task. First, to *distinguish* the fully reprogrammed colonies of iPSCs from those partially reprogrammed (which are thus *not* pluripotent). Second, to *predict* such outcome at an

[1] Notably, at the beginning of the project the Japanese corporation owned a 30% stake in the small company, and thus had close connections with it, and an inherent interest in the latter's success in developing a marketable product. As the project evolved, however, the corporation decided to pursue a different path, and started, in parallel with the small company, the development of a competing technology of its own.

earlier time point than the standard time (one month) needed by scientists, thus allowing the anticipation of the colony selection procedure (see chapter 2).

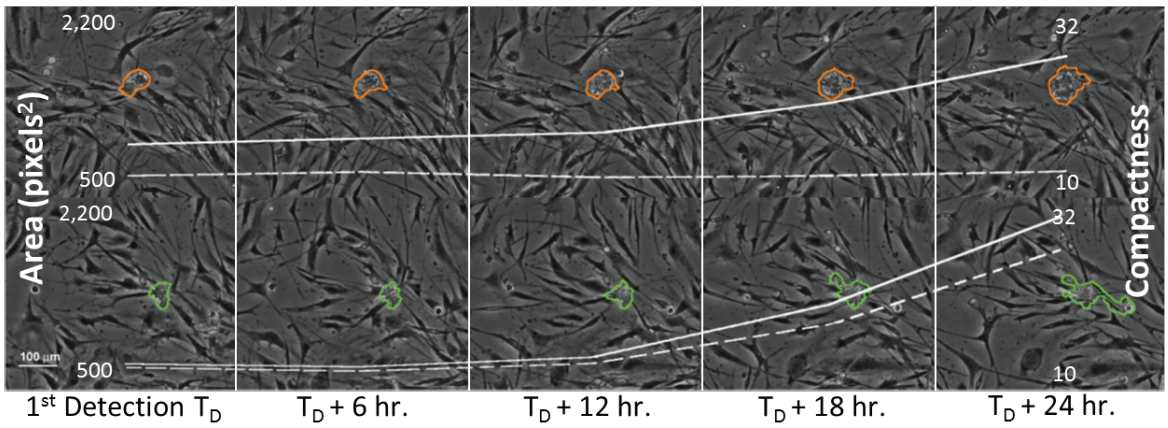



**Figure 15. Software–based pluripotency assessment.**

Furthermore, issues of *consistency* were also at stake, for the automated system was predicted to produce less line–to–line variation in expression of pluripotency markers, with respect to that entailed by the standard visual inspection and manual selection of colonies by experienced scientists. Consider for instance the following exchange occurring at a project meeting:

> iPS Core leader: *you'll see how there is really much more difference among persons than with the machine. It's like having in one case one umpire calling the strikes, whereas if you have different umpires calling the strikes, you'll see how they tend to call the strikes in different ways. Even though it should be one strike zone, everyone has got its own strike zone.*
>
> Harvard scientist: *...exactly. The expert person cannot be everywhere, [the head of the Core] cannot be everywhere, and do all the reprogramming on her own, but the machine can in fact be everywhere! That's the difference.*

Moreover, the specific objectives for the different participants in the AP differed. From the perspective of the iPS Core, the reason for engaging in collaboration with the small bio–imaging company was to leverage on the latter's expertise in order to develop an

automated system, potentially suited for adoption by the Core in its daily operations. The rationale for undertaking the path of automation was twofold, and related to the need to decrease hands–on costs while increasing throughput, thus achieving an economy of scale (by the end of 2014 the Core was still being partially subsidized by HSCI funds), and to establish an experimental infrastructure geared to keep up with the large scale studies that increasingly dominate the landscape of iPSC research. In the words of the leader of the iPS Core:

> *More and more groups are contemplating larger and larger studies, and if we don't have the capacity to engage them for those studies, then our Core will be left in sort of the Medieval time of iPSC production, we won't be a Core that front edge these things any more.*
>
> *When you automate and you have people that start to make a very consistent product like this, is not going to be cost-effective any more to do it in house, and you are usually producing something of usually substandard value. So because how cheap and easy is that someone else is making it, optimizing scale, if you doit manually in your lab it would be like Stone Age, you know, trying to carve things with stones… So if you build a better automation, a better process, you are more efficient, you are going to increase the stream of revenue you generate, so that you can make over the course of a year 5.000 cell lines, and then it turns to 10.000, and that increase the revenue […]. I think this is the main reason, driving down costs and increasing capacity. It's true for our Core, too.*
>
> Interviews with iPS Core leader

For the small company, and its Japanese partner, the goal of the project was, first, to establish links with a world–renown iPSC lab, Harvard's iPS Core, thus being able to rely on SBIR grant money to test and develop one of their products. Explained in November 2013 the main representative of the small company involved in the project that:

*So what's pushes the envelope... this collaboration was lubricated by NIH (through a SBIR grant), and we discovered from our business model that it is really an excellent way to do business, the RandD money gets us into top labs, when we get exposed to top companies, like [multinational corporation] and Millipore. We know how to write grants, we have collaboration with [multinational corporation], so now we are able to propose grants to the best academic labs in the country, and the money from the government facilitates this collaboration.*

Interview with vice president, small company

The second objective of the small company was, consequently, to leverage on the iPS Core's expertise in order to test for a new bio–imaging system to be commercialized among iPSC research laboratories worldwide. This product was envisioned as not only meeting the growing demand of a growing market, but also as facilitating the very consolidation of the market itself:

*In the future - and the future is now - people will need to create lot of cells lines. In the process of automating the cell line production, a high value step is the selection of the fully reprogrammed clones and the identification of those clones (it is the most technically challenging aspect of stem cell scientists). Then, colonies need to be characterized, which is extensive. So, rationale of the project is, what if we can tell through video image analysis which one to reprogram. If you have a computer which can tell this one is fully reprogrammed so you can pick it, it would be a much simpler process.*

*[…] The reality is, it takes a lot of effort to make something work well. Now we want to get something that works really robustly and reliably, and this is something not trivial. What we are doing is paradigm changer. If we manage to get it, the whole field will shift and say yes, we want microscopy, and all of the sudden we'll have lot customers. We have proved the principle, now we have to prove the product. If it works*

*for Sendai...it won't be optimal product, but there will be customers, there will be lot of demand, people will take you seriously, and you'll have a business (now it's just research).*

Interview with vice president, small company

### 5.2.2 The project inception: negotiating requirements.

Differently from NYSCF, that in reason of its sheer financial capacity developed its own automated infrastructure internally, according to its own requirements (and by retaining the services of an engineer from the leading company in the field of cell–based automation, Hamilton Robotics, who, after extensive collaboration with NYSCF in the initial set–up phase of the GSCA, was hired by the organization in 2012), the way the AP evolved owed to its *collaborative* nature among different actors within the framework of the SBIR grant.

For one thing, at the beginning of the AP, iPS Core scientists and representatives of the company had different ideas concerning the optimal project outcomes. Notably, two different approaches emerged with regard to the functions to be performed by the bio–imaging software. For iPS Core scientists the usefulness of the new system relied, consistently with its standard experimental practice, on its ability to predict whether a cell colony in formation would have actually become a colony of *pluripotent* cells. For such purpose, a *binary outcome* was all that the system should have provided:

Head of iPS Core: *What you really want is [the] difference between pluripotent/not pluripotent cell, yes or no. Forget all the rest...*

For the small company, it was instead the system's ability to predict the colony *differentiation* potential, i.e. its amenability to be differentiated into a specific cell type of

interest, that was seen as the main selling point to potential customers. As the company's vice president explained to me:

> *If you can understand things that humans cannot understand… that's nice if you are trying to sell something! Those guys can pick [colonies] very well at three weeks, but if all of a sudden I can tell them "if you use my software, I can give you the colonies that are a bit better in expansion... Given that these ten colonies are iPSCs, I can tell you which ones are gonna be better to be differentiated…" this type of things is not easy to see by eye, so it gives my software a good reason for someone to purchase it.*
>
> Interview with vice president, small company

These contrasting views about the issue surfaced repeatedly during project meetings. Consider for instance the following exchange:

Head of iPS Core: *we usually wait for picking until the end of the reprogramming, to be more sure, and we look at the morphology of the cells. But if the software can tell us that a colony is a good one after two weeks, we can pick the colony then!*

Company's VP: *In addition, we can also give you a scorecard. The idea is, with regard to the product we want to sell, other than say yes or no with regard to pluripotency, it can also tell us about how the cell will differentiate…*

Head of iPS Core: *no, it must be yes or no! For the software, we just want to know the pluripotency, yes or no.*

Company's VP: *Right, but the score can tell us something more…*

Head of iPS Core: *it must be yes or no! Here at the Core we do the differentiation into the three germ layers to assess pluripotency. Looking at the differentiation bias is a completely different thing, it could be useful for users, but it is not what we are interested here at the Core, it's a different type of info…*

Eventually, the issue was settled by opportunity and marketing considerations. Over the course of the project, representatives from the company and iPS Core scientists progressively converged on one point. The system had to meet two requirements. First, it should have been amenable to being commercialized to a wide variety of customers (mainly research labs); second, and consequently, it should have been something "radically simpler" (interview with head of iPS Core) than NYSCF's GSCA – and that entailed dropping the differentiation prediction part, due to the burdensome data processing and dedicated equipment needed to make it workable for customers. In the words of the small company's VP:

> *Early automation systems, which you see at NYSCF, are fairly complicated - lot of handling of the cells, going from plaiting system to suspension to FACS sorting, using fluorescence markers… So, practically speaking, if we could tell what are the good colonies just by watching how they form, we will be able to engineer a much simpler automation system, which would not require specific equipment, could be a lot cheaper than the first generation system and be much more easily commercialized. It's a race!*
>
> Interview with vice president, small company

### 5.2.3 Building momentum in the project.

Continuous references and comparisons with NYSCF's GSCA were a constant throughout the project. In many significant respects, the automated system being developed differed considerably from that of NYSCF, and programmatically so.

In the case of NYSCF, the automated system was the cornerstone of its centralization strategy, aimed at accruing agency within the organization. In light of its sheer complexity (e.g. the nine modules of the system occupy several rooms in NYSCF's laboratory) and operating costs (all its components are customized), the GSCA was not meant to be integrated within standard experimental practices in the field of iPSC research. Rather, as

we have observed with regard to the introduction of a new protocol for iPSC derivation, the GSCA gives material currency to NYSCF's disruptive innovation approach, for it introduces new experimental standards of its own. As remarked by the CEO of the organization:

> *It is a huge amount of resources to do this, so what we don't want to do is to have something like VHS and Betamax, these competing platforms. What we would like to do is to have* this *automation be the automation that is used in the field.*
>
> Interview with CEO, NYSCF

On the contrary, *integration* was the keyword for participants in the AP, whereby the bio–imaging system was being developed so as to meet a twofold requirement: the widespread commercialization of the bio–imaging software itself among iPSC research laboratories, and the consistency of the cell lines being reprogrammed by means of the bio–imaging technology with established standards in the field, in order to meet the requirements of the Core's customer base, and thus allow its adoption by the Core in its routine operations.

Notably, the latter requirement of integrating the automated system into the Core's standard experimental practice led to the development of a bio–imaging software aimed at *mimicking* as closely as possible the operation of visual selection performed by skilled scientists. As iPS Core scientists argued in the following exchange:

> iPS Core scientist 1: *If you have the software that can do what you can do with your eyes it would be great!*
>
> iPS Core scientist 2: *...The machine is a bit like us, hopefully better at recognizing earlier.*

Accordingly, whereas NYSCF's approach resulted in the development of a magnetic cell sorting system, that disaggregates the colony of cells into single cells unit (see previous chapter), the bio–imaging software being developed in the AP relied on the *quantification of morphological parameters* typically assessed visually by scientists, such

as the density of cells, and the speed of cell growth, that could be predictive of pluripotent colonies formation.

Furthermore, this translates, in experimental terms, with the preservation of the standard 'clonal' reprogramming of colonies (whereby, to physically select iPSCs, suitable colonies are picked up with a pipette and transferred to a new culture well for subsequent culture expansion, in which the 'progeny' is derived from the same parental cell, and is thus clonally derived[2]). In the case of NYSCF's GSCA, on the contrary, colonies are disaggregated, cells are individually sorted for pluripotency markers, and finally pooled together leading to a mixed (and thus polyclonal) population of cells (for 'progeny cells' are not derived from the same clone). Observed the leader of the iPS Core in the course of a project meeting:

> iPS Core leader: *The main claim of NYSCF is standardization. But if it's full automation, you have to make concessions. Their population changes over time, because it's not clonal. Over time, once clones are stabilized, they are more stable, and that is because one clone grows a little bit faster, and after a while it takes over the whole population. If you go clonal, you already know that, that each clone is different, and that's why you compare more clones! NYSCF sold to half of the world that their platform is more consistent, but that's not really true. Hence: if you guys can manage to do this, your system would be definitely better.*
>
> HSCI scientist: *…this is what NYSCF says, that the robot is better than the experts at picking.*
>
> iPS Core leader: *The great pushback against NYSCF is that their system is non-clonal, and people don't like that… So there is also another possibility for the system you are developing, which is of selling it to them!* [laughs]

[2] For a comparative analysis of clonal vs non clonal reprogramming, see Willmann et al. 2013.

| | The Global Stem Cell Array (NYSCF) | Bio–imaging software (Automation Project) |
|---|---|---|
| ***System development*** | Internal | Collaboration within SBIR framework |
| ***Automation of manual protocol*** | Protocol reconfiguration (magnetic cell sorting) | Mimicking visual assessment (morphology–based) |
| ***Reprogramming type*** | Single cell (non clonal) | Colony of cells (clonal) |
| ***End product(s)*** | iPSCs and differentiated cells | – iPSCs<br>– Bio–imaging software |
| ***Stages to be automated*** | Full automation (from iPSCs derivation to differentiation) | Pluripotency assessment (iPSC colony selection) |

**Table 2. Main differences between NYSCF's GSCA and automated system being developed in the AP.**

### 5.2.4 The end of the project.

Table 1 provides a synoptic overview of the main differences between NYSCF's GSCA and the system being developed in the AP. As we have observed, not only the developing process diverged in significant ways, entailing the involvement of different constituencies on an equal footing; but also, the need for participants to negotiate requirements was brought to bear on the project's outcomes.

Ironically, in the end, the two requirements of producing a widely commercializable system, and also one that could be easily integrated in standard scientific practice, thus meeting the needs of iPS Core scientists, proved to be conflicting. For the need to design a system simple enough to be amenable to widespread commercialization among iPSC scientists, was also the very reason that could potentially undermine adoption by the Core. Let me elucidate this point by means of comparison.

The sheer complexity of NYSCF's system, that which obviously hinders its commercialization as a product *in se*, was also what greatly enhanced its usability. Not only is GSCA's cell sorting system able to predict iPSC's differentiation propensity; also, it works in conjunction with a robotic handler that fully automates the whole operation,

without human intervention, thus greatly streamlining the process of iPSC derivation, expansion and differentiation.

The system being developed in the AP, on the contrary, was not meant to predict iPSCs' differentiation propensity, for this would have required *ad hoc* instrumentation, to perform the data analysis, that is not widely available in the standard iPSC research lab; also, it was not supposed to have a robotic machine for picking colonies, for this would have required integration with specific instrumentation similarly not available in iPSC labs. As a whole, while these two features were geared to facilitating its adoption by iPSC research labs, the latter in particular was, at the same time, causes of concerns for iPS Core scientists. Consider the following exchanges:

> iPS Core scientist 1: *It took a very long time to do something that we do very quickly... without a robot for picking, this technology will be useless!*
>
> iPS Core scientist 2: *It took us a week, once we received the images of the colonies to pick from [the company], to… actually pick them! It is difficult, because you have to look at the image, then look for the colony in the Petri dish, but then during the time it takes for the software to do the analysis the colony has grown, it has moved… and then you have to find it…*
>
> Head of the Core: *it's hours and hours to do what usually we do in two seconds!*

As of June 2015, participants to the project are confident of having obtained enough data to support the claim that the software being developed is able to predict iPS colony formation in advance than the standard month needed for reprogramming. Building on that, they are working on putting together a second grant application in order to further the development of their automated system into a viable product (field notes 2015).

## 5.3 Conclusions.

In this chapter, I have attended to the progressive entrenchment of stem cell research at a bastion of American academic research, Harvard University, by focusing on the establishment of the Harvard Stem Cell Institute and the iPS Core facility. While similarly advancing a translational stem cell research agenda, HSCI and the iPS Core maintain in many significant respects a different approach from the one, outlined in the previous chapter, embodied by NYSCF. Whereas NYSCF, driven by philanthropic constituencies, set out to adopt a disruptive mode of innovation, HSCI's endeavor, governed by some of the most prominent scientists in the field, is aimed at sustaining established research practices in the field of stem cell research. The two institutions' different approaches to automation, I contend, nicely capture and epitomize these differences.

I will reflect more in depth on these points of divergence – as well as some other points of convergence – in the concluding part of the dissertation. Before I do so, I shift from the American to the European context, and move to the third platform on which this dissertation focuses, the European Bank for induced Pluripotent Stem Cells.

# Chapter 6. The European Bank for induced Pluripotent Stem Cells

The European Union is undergoing profound transitions. Strategic geopolitical challenges, ranging from the disputed trans–Atlantic trade agreement to the rise of intense political instability within and across its borders; grandiose yet seemingly ineffective programs to prop up its ailing economy vis–à–vis a largely self–inflicted and unrelenting crisis; and ongoing contestations about the lack of democratic credentials of its founding treaties and institutions: all these elements define the contours of a critical identity challenge.

This appears to be especially true with regard to the current economic crisis, where a look at the statistics makes an uncomfortable reading. Unemployment rates within the European Union soared by more than 4% between 2008 and 2013 to reach the 11% threshold (12.1% in the eurozone), meaning that a staggering number of 26 million people are forcibly out of work in Europe at the moment (as of 2014). In countries like Spain, Croatia and Greece (with Italy and Portugal not far behind), more than half of the population under 25 is currently unemployed. As of 2011, one in four people in the EU experiences poverty or social exclusion, with persistent wide inequalities in the distribution of income across and within the member states (source: Eurostat). The economic crisis have made its toll felt on health, too: the strained Southern-European countries, Greece in particular, are witnessing outbreaks of HIV and infectious diseases (due to impaired access to care and prevention), and rise in prevalence of psychological problems and suicides rates (Karanikolos et al. 2013). Moreover, what numbers are not able to capture, and in fact

often conceal under their detached objectivity, are the many disrupted lives, the nihilistic sense of unfulfillment, and the disbelief and anger pervading whole generations.

Once a bastion of wealth and well-being, the European Union is now facing unprecedented struggles, threatening to turn it into a state of disarray. Most notably, what is evidently at stake, in the present situation, is not only its prosperity and global geopolitical role, but also, and more profoundly, the still unresolved issue concerning its identity as a supranational political entity: what does 'Europe' refer to, and what are the sources of 'Europeness'?

Unsurprisingly, especially for a continent that proclaims to embrace a knowledge-driven economy (as for the 'Lisbon Strategy', 2004; and the 'Europe2020 Strategy', 2010), the ubiquitous presence of science and technology dominates the rugged landscape in which political agency is deployed, contested and renegotiated. Most notably, the life sciences and biotechnology, in reason of the innovation potential they entail, are increasingly being recruited to frame the basic elements of the supranational order–in–the–making.

In particular, both the intertwinement of biotechnology and capital that goes under the rubric of 'bioeconomy', and the push to the accelerated commercialization of laboratory breakthroughs (that represent, in many respects, two sides of the same coin), have emerged as linchpins around which the new supranational socio–political–economic order is imagined, negotiated and enacted. Conspicuous testament to this is the launch of the 'Bioeconomy for Europe' strategy in 2012, which is geared to leverage the "set of economic activities relating to the invention, development, production and use of biological products and processes" to "comprehensively address inter-connected societal challenges such as food security, natural resource scarcity, fossil resource dependence and climate change, while achieving sustainable economic growth" (European Commission 2012); and – most prominently – the mobilization of health– and biotechnology–related

programs in the Horizon2020 funding scheme, which is a mainstay of the ‘Europe2020 strategy’ (with nearly €80 billion of funding available over 7 years, from 2014 to 2020, of which the life sciences hold the lion share), aimed at fostering innovation, by “taking ideas from the lab to the market” (EC 2015), and thus securing Europe's global competitiveness.

At the same time, while undoubtedly growing in relevance in recent times, the mobilization of biotechnology as an important component of the European institutional architecture has deeper-rooted origins.

As argued by Gusmão (2001), the incremental process of European integration is strictly related to the construction of a ‘European research community’, through the progressive implementation of various structures and funding schemes that have propelled the emergence of research strategies that extend across national frontiers. While in fact, Aguilar and colleagues (2013) similarly observe, in the mid–1970s there was no such a thing as a common ‘research and innovation policy’ at the European level, efforts spearheaded by a relatively small number of individuals within the EU institutions led to the launch, in the early 1980s, of the ‘Biomolecular Engineering Program’ (1982–1986), which, in turn, paved the way to the consolidation of a ‘European supported Biotechnology’. In a similar vain, Sheila Jasanoff (2005) contended from an STS perspective that the contested consolidation of Europe as a unified political space (in spite of the opacity of most of its technocratic institutions and the lack of an 'imagined community' (Anderson 1983) of European citizens withstanding the efforts at integration) owed not only to major institutional developments, but also to the identification of biotechnology as a key area for policy intervention, and the contextual framing of a 'European way’ to biotechnology. "Some twenty-five years of European biotechnology policies", wrote Jasanoff in 2005, should be seen "as both shaping and shaped by European politics". On the one hand, she argues, "like nineteenth-century nation-states, the EU has found it necessary to specify the problems it wanted to solve in order to consolidate and

legitimate its political existence", with those issues revolving around the regulation of biotechnology figuring prominently among them. Conversely, to address the “seemingly technical question” of the stabilization of biotechnology, ”it proved necessary to address what kind of union Europe was - or wanted to be - both in relation to its members states and as a player on the world stage“ (Jasanoff 2005).

Against this backdrop, in this chapter I seek to provide an empirically sensitive account of how a specific instantiation of the push to biotechnology–driven innovation, namely translational induced Pluripotent Stem Cell research, is enrolled and mobilized in the current process of renegotiation of the ‘European’ socio–economic–political identity.

In particular, I will focus on the revealing case study of the European Bank for induced Pluripotent Stem Cells (EBiSC), established in 2014 within the framework of the Innovative Medicines Initiative (IMI). Drawing from documentary sources and recent ethnographic fieldwork, I expound how, through the mobilization of an innovative biomedical platform, structured around a public–private partnership model of governance, the stabilization of a new and enticing field of research is co-produced along with the structuring of a significant portion of the European science policy. On this basis I then move to interrogate how the priorities of this program construe an envisioned European (public) good with its attending beneficiaries, through a distinctive choreography of actors and participatory resources.

## 6.1 The Innovative Medicines Initiative.

The European Bank for Induced Pluripotent Stem Cell was established, in 2014, within the framework of the Innovative Medicines Initiative (IMI). In many significant respects, the latter decisively influenced the development of the former, and thus deserves its fair share of analytic scrutiny.

IMI was established in 2008 as a public–private partnership (PPP) – the world's largest in the life sciences – coupling the European Commission and the European Federation of Pharmaceutical Industries and Associations (EFPIA), the trade association of pharmaceutical corporations operating in Europe. By fostering collaborative endeavors between academia and the pharmaceutical industry, the fundamental aim pursued by IMI, very much in line with the core of the translational narrative, has been to "speed up the development of, and patient access to, innovative medicines, particularly in areas where there is an unmet medical or social need" (IMI 2015).

IMI's establishment owes to the legal act on IMI, adopted by the European Council in December 2007, and published in the Official Journal of the European Union in February 2008 as a Council Regulation setting up the 'Joint Undertaking for the Implementation of the Joint Technology Initiative on Innovative Medicines' (EurLex 2008; Kamel et al. 2008). In light of such provision, IMI was set up with its own legal entity based in Brussels, in premises situated within the Ixelles quarter, a stone's throw from the offices of the European Commission.


**Figure 16. IMI Headquarters, Ixelles, Brussels, Belgium.**

Historically, the development of IMI is rooted in the European Technology Platforms (ETPs), launched within the 6th Framework Program (FP6, 2002–2006) of the EC, with the aim of establishing industry-led stakeholder *fora* that could devise and develop research and innovation agendas at EU and national level to be supported by both private and public funding (EC 2015a). A first step in the set up of collaborative endeavors between institutional and private actors, the ETPs further led to the establishment, within the 7th Framework Program (FP7, 2007–2013), of the Joint Technology Initiatives (JTIs). Cementing a more formal partnership between the EC and the industry of a given sector, the JTIs were a means to implement the Strategic Research Agendas (SRAs) of a limited number of ETPs, whose scale and scope of the objectives required a dedicated governance mechanism, that the various ETPs were not able to provide (EC 2015b). Stemming from various pilot projects launched within FP6, IMI was formally launched as a JTI in 2008. As observed by an IMI representative:

> *IMI was a bet, something absolutely innovative in the political landscape of the time, in the relationship between industry and the EC. Apparently, IMI had a great return, so much that the EC wanted to invest more. There was a lot of interest towards IMI. IMI strived to obtain visibility and credibility, and apparently, today, that goal has been reached. Possibly, among the JTIs, IMI is the one that reached the higher visibility, which was among the key objectives set forth by the governing board of the EC and EFPIA.*
>
> Interview with IMI representative

Notwithstanding its continuity in scope and governance, the development of IMI occurred in two distinct phases. The first phase was the so–called (retrospectively) IMI1, which lasted from 2008 to 2013, and coupled in collaborative endeavors various academic institutions and EFPIA–members companies. Within the framework of IMI1 around 40

collaborative projects, for the most part still ongoing, have been launched (EBiSC being one of them), in areas spanning from antibiotic resistance to cancer. Overall endowment of the program was €2 billion – €1 billion each from the European Union and the pharmaceutical industry through EFPIA. Crucially, as I will expound below, while the public contribution is in cash, the contribution of the industry occurs through 'in kind' provisions. That is, EFPIA members involved in IMI projects contribute to the overall budget by providing their own equipment, resources and staff time.

Building on the experience of IMI1, IMI2 was launched in 2014, within the framework of Horizon2020, with an increased overall endowment of €3.3 billion, and a prolonged timeframe of six years (it will last until 2020). While for most parts it follows in the footsteps of the previous program, IMI2 maintains two important differences with respect to its progenitor. First, its projects are more translation–oriented, and cover areas of research that are closer to clinical application (thus shifting the projects' focus from biomarkers, data management, pre-clinical stage to proof-of-concepts clinical investigations, patients recruitment, phase II/III trials). Second, it involves the added participations of actors other than academia and the pharmaceutical industry, such as small and medium enterprises (SMEs) and non–profit organizations.

## 6.2 IMI's translational goals.

The overarching strategy of IMI1 was outlined in a Strategic Research Agenda (SRA) of IMI (SRA of IMI 2005), which was developed since 2005 by the Research Directorate of the EC and EFPIA through consultations that included stakeholders such as academic scientists, regulatory authorities and patient groups (Kamel et al. 2008). The scope and goals of IMI2 were similarly defined through the issue, in Spring 2014, following a similar path of consultations, of the Strategic Research Agenda of IMI2 (SRA of IMI2 2014).

While framing issues in slightly different ways (whose detailed analysis transcends the scope of this dissertation), the two agendas advance largely coinciding priorities. In

particular, both re-produce and articulate a well establish "discursive code" (Gottweiss 1998) the ties together the acceleration of clinical translation to industrial growth and the capitalization of the biotechnologies, where the urgency for action at EU level stems from a purported lag vis-à-vis the US:

> *The mission of the Innovative Medicines Initiative (IMI) is to contribute to creating biomedical research and development (RandD) leadership for Europe to benefit patients and society. To this end the two key aims of IMI are to support the faster discovery and development of better medicines for patients and to enhance Europe's competitiveness* (SRA of IMI).

> *The United States of America remains dominant in the field of health and life sciences. The US therefore remains an attractive destination for researchers resulting in the 'brain drain' from Europe. The rapidly expanding science base of emerging economies such as Brazil, China and India further exacerbates this issue. It is therefore essential that Europe continue to drive innovation in order to remain competitive in biomedical research* (SRA of IMI2).

As the primary means to achieve this twofold objective, the SRAs point to the need of an organization gearshift centered on the establishment of linkages among public and private actors, and the design of a governance model, the PPP, that builds on the seamless flow of knowledge between the academic and industrial domains.

Hence, IMI represents a paradigmatic instantiation of organizational innovation implemented to accelerate the pace clinical translation (see chapter 1). As such, it follows in the footsteps of similar initiatives pioneered in the US a few years earlier. In 2004, following publication of an influential report on Stagnation/Innovation, the FDA launched its Critical Path Initiative, as a means to implement public-private partnerships (PPP) to share data, expertise, and resources in order "drive innovation in the scientific processes through which medical products are developed, evaluated, and manufactured" (FDA 2004;

Goldman 2012). To this end, the C-Path Institute was created. An Arizona-based non-profit body, the institute was meant to support this initiative by fostering collaborations between industry, academia and regulators. Funding sources were varied and included grant funding from the FDA, fees from participating member organizations, donations from private and philanthropic organizations (Goldman 2012).

Around the same time, as an outgrow of the NIH Roadmap (analyzed in chapter 1), the NIH initiated its Public-Private Partnership program, with the goal of developing an advisory support with various non-governmental organizations, such as industry, foundations, and advocacy organizations, in setting up complex, multi-sector arrangements oriented to the acceleration of translation of laboratory research findings.

## 6.3 The rise of Public–Private Partnerships as public policy tools.

Enjoying remarkable acclaim in both official and scholarly circles, *Public-Private Partnerships* gathered momentum in the political *milieu* of the 1980s, and have since become a widespread public policy tool, increasingly endorsed at the EU level (Kinnock 1995), to structure relationships between the public and private sectors. Normatively, the implementation of PPPs draws from two conceptual and ideological referents.

First, PPPs are frequently viewed as epitomes of the neoliberal turn of the 1980s, when, under the ascendancy of the Thatcher and Reagan governments in the UK and the US, free-market advocates and conservative politicians joined in common cause against the liberal welfare state, promoting a marketization agenda consisting of market promotion and state-shrinking provisions (i.e. public asset sales, outsourcing, divestitures) (Starr 1998; Harvey 2005).

However, while at first sight the implementation of PPPs might appear as a by-product of the privatization movement, aimed at stretching one sector by shrinking the other, its relationship with it is actually more nuanced.

For one thing, partnerships often represent a strategic fallback option, in areas where full privatization seemed less tractable (for instance due to technical problems attending the assignment of property rights), feasible or even desirable (as it is the case with the capital-intensive projects of the biomedical sector). As Linder notes (Linder 1999):

> *[PPPs] have been viewed as a retreat from the hard-line advocacy of privatization. From this perspective, they serve a strategic purpose, enlisting the support of more moderate elements that are less opposed to state action on principle. Partnerships are accomodationist; they hold back the specter of wholesale divestiture and, in exchange, promise lucrative collaborations with the state.*

Moreover, the hallmark of PPPs is *cooperation*, not competition. As such, the establishment of partnerships maintains a key difference from outright privatization: rather than *shifting* the boundaries of the public and the private, with the former inevitably ceding ground to the latter, PPPs set out to *blur* them, eliding "demarcations that defined roles and set the rules of engagement between business and government since the Progressive Era" (Linder 1999). Hence, partnerships remove the adversarial character of the public-private interaction, and *confound* the points of reference defining this binary separation (insofar as they require actors from each sector to adopt points of view that used to define the identities of their counterparts, and, in so doing, to *redefine* their own identity). Accordingly, as Linder argues (Linder 1999):

> *"to say that partnerships are yet another anti-liberal effort to shrink the state by privatizing its functions is to misconstrue the significance of the partnership idea. [... F]iguratively stretching one sector by shrinking the other simply no longer applies (if it ever did) because the meaning of the sectors themselves, through the partnership, is shifting."*

Therefore, as a number of scholars have observed (Ferlie et al. 1996; Joldersma and Winter 2002; Skelcher 2005), PPPs are inherent *hybrid* entities, and, as such, they

represent a paradigmatic instantiation of the *socio–economic hybridity* that defines biomedical platforms (see chapter 3). As "contingent settlements between plural institutional logics within one organizational entity" (Skelcher and Smith 2013), not only do PPPs combine the features and organizing principles of public and private sector actors; more radically, they develop a "*blended* hybrid model that adapts or moves beyond [them]" (Skelcher and Smith 2013, *italics mine*).

A second normative influence on the design and implementation of PPPs comes from the management prescriptions coalescing under the *New Public Management* rubric (which in itself largely draws from the same neoliberal ideological background) (Pollit, van Thiel and Homburg 2007).

Conceived as one among a number of management reforms (such as the development of performance indicators and result-oriented processes, the disentangling of administration from policy, the implementation of contract-like relationship, the adoption of a client-service *ethos*), partnerships are seen as a tool that could normalize the governance of the public sector on private sector models. Exposing the public sector to the market constraints that "discipline" the functioning of businesses, so the argument goes, would change the way the former functions, while promoting efficiency gains without divesting from it altogether.

Seen from this perspective, however, the collaboration "resembles more of a mentoring relationship than a joint undertaking. The flow of know-how appears asymmetric. Government managers are expected to become more like their business counterparts, rather than viceversa" (Linder 1999).

While the sets of proposed reforms are largely the same in different political and cultural contexts, the practical realization of PPPs differs, according to the specific aims and the local circumstances underpinning their implementation.

For one thing, the mechanisms of legitimacy differ. For instance, while in some political contexts PPPs arise as a mean to reduce the public sector footprint, and are hence conceived as an opportunity to lessen state interference, in others they are seen as a mean to achieve new solutions for existent problems through a *joined-up government* of public and private actors parties (Pollit, van Thiel and Homburg 2007).

Moreover, according to the different aims being pursued, PPPs can be implemented in different ways. Among the different institutional forms PPPs can take are *contracting out* models, in which the public sector contracts out the provision of a service to a business or non-profit organization deemed to offer a higher quality solution at lower costs; *joint ventures*, aimed at financing public infrastructure projects with private capital; *public leverage* models, in which governments maintain a strong steering function, deploying their legal and financial resources to foster the alignment of private sector's activities with public policy goals; and *strategic partnership*, in which "there is boundarylessness in terms of the distinctions between the constituent parties" (Skelcher 2005): partnerships are here intended to yield mutual beneficial outcomes, and to cement a collaborative endeavor between public and private actors on a trust-based relationship and joint decision-making basis. Both the latter cases are highly relevant insofar as they represent some of the most employed forms of PPPs in the life sciences, where both strong ethical concerns, the intensity of capital required to set up projects, as well as a tradition that sees science as a public good have prevented a complete privatization of its underpinning research structures.

Building on the growing endorsement attributed at EU level to PPPs (Kinnock 1995), IMI was shaped on this governance and organizational template. Drawing from this general overview of the key tenets of PPPs, I now move to account for IMI's specific configuration, and how the latter is brought to bear on stem cell research practice at the European level.

## 6.4 "Having a structuring effect on Europe": creating a unified EU research landscape.

Speaking at the IMI Stakeholders Forum held in Brussels in May 2014, Aidan Courtney, CEO of Roslin Cells, a leading partner in the EBiSC consortium, put himself in the analyst's shoes to conceptualize the sociotechnical imaginary (Jasanoff and Kim 2009, 2015) being articulated through IMI's endeavor. As he said (Courtney 2014):

> *IMI projects are big. And we are here not just to deliver the research, but actually to have a structuring effect on Europe, and change the way we do research in Europe*.

As I have previously observed, the notion of mobilizing both public and private funding at European level to consolidate a European research community is not new, and dates back to the mid-1970s (Gusmão 2001; Aguilar et al. 2013). What changes here are thus the distinctive resources being drawn upon in the implementation of the program; its specific objectives; the way agency and control are allocated among actors. In what follows, I expound IMI's performativity in shaping a significant portion of European–supported biotechnology. In particular, I contend that IMI's envisioned "structuring effect" is brought to bear on both the *macro–level* of IMI's governance structure, and the *micro–level* of iPSC research practice.

First, consistent with the PPP template sketched above, IMI is aimed at tracing *a new geography of European biomedical research*, so as to create a "truly unified space" (field notes 2015) of science and technology at the European level, overcoming a longstanding fragmentation of the main (academic and industrial) actors involved in it. As explained by the principal scientific officer at the DG Research and Innovation of the European Commission:

*The main aim is to have people from different countries and institutions working together, to avoid wasting money, repeating some of the infrastructures, etc. That is one of the key features for the EU policy and for getting things going…*

Interview with principal scientific officer, DG Research and Innovation, EC

The establishment of this new European scientific and technological 'space' was achieved through a number of reconfigurations of entrenched arrangements. First, it proceeded by significantly altering the process of biomedical knowledge–production, through the reconfiguration of the identities, roles and functions performed by industrial and academic actors. On the one hand, whereas in common conceptions of RandD pipelines the pharmaceutical industry traditionally focuses on the 'development' stage of a product, i.e. on the translation of lab–generated knowledge into a commercializable therapy, in the IMI framework the industry is instead prompted to play a first hand role in the generation of that early–stage knowledge itself. For, early industry involvement in the process of knowledge–production is seen as conducive to generate a kind of knowledge that could be then more easily translated into clinical products. As an IMI representative observed:

*The goal of the IMI program was precisely to sustain the development of a new knowledge at the industrial level, since it was noticed that, otherwise, there was no meaningful progress... There is no doubt that this program has been conceived to help the industry bringing forward the thresholds of knowledge.*

Interview with IMI representative

Conversely, the reconfiguration brought forth by IMI projects requires that European academia, through sustained interaction with the pharmaceutical industry, develops its own capacity to become akin to its American counterpart, so as to exploit commercially the knowledge it generates. In the words of an EBiSC partner, IMI was conceived as an

"emergency procedure" intended to make European academia a site of innovation in its own right:

> *I think academia in Europe still does not see the whole of the translational chain. It is basic research, but it does not go all the way towards the clinic, towards commercial exploitation. Universities in Europe don't have functional TT units. If a professor comes up with something worth of commercial exploitation, it's complex, there is not the infrastructure in play, the translation still doesn't work very well. In the US they are much more professionalized. The IMI projects are supposed to be a way to stop this…. I think there was a feeling at the EU level that initiatives put in place in the past [to foster commercialization of academic research] were not done efficiently. Universities have the knowledge, but they don't exploit that efficiently. IMI-funded projects are then something like an emergency procedure.*
>
> Interview with partner in IMI's project

These points concerning the need for creating stronger linkages between public and private actors, while reconfiguring their identities in the process, are stressed by EU functionaries themselves. Recalling the evolution of the EU science policy landscape in the last decade, an official from the EC observes that:

> *Personally, I think that 10-15 yrs ago, in the early days, the industrial–manufacturing landscape in the EU was quite different. The idea was, if academia comes up with good ideas, they would have been picked up by industry and developed. And there was almost a kind of antipathy between academia and the industry. But what we have seen is that at the EU level the resources going into biomedical research have increased in recent years through the different framework programs, largely because of the EU parliament and their influence, and they are representing the citizens of EU, who wants to see something back for their investment. To demonstrate that money is justified we need to see something come out of it - and the upstream, more fundamental*

*part of research is seen as a bit of a luxury. That's been the reason. Now the whole debate about the EU project, referenda being in the balance in some cases... So the trend, the driver, has been to connect more with citizens, and try to get something out of it. That's my take on the change in emphasis...*

*On the luxury side, this is the public perception of scientists in academic/public labs in today's cold, wintery world in Northern Europe, that they have got a nice lab, a permanent staff, they are doing something which they like, it's probably their hobby. In contrast to the precarious world outside...*

Interview with principal scientific officer, DG Research and Innovation, EC

Furthermore, a second feature of the redefinition of the European research landscape is the alleged creation of *boundaries internal to the pharmaceutical industry* itself. A main requirement of the IMI grant agreement, signed by EFPIA and the EC, is indeed that only costs sustained within the European Union and partner countries (such as Switzerland) are eligible for IMI funding. In turn, this requirement underpins the framing of something like the *'European' pharmaceutical industry*, i.e. the creation of a (supra)national identity and citizenship for quintessentially global institutions, registered overseas, operating on global markets on a trans-continental scale. However, this framing plays out more as a *legitimacy strategy* for justifying funding, rather than an effective provision for enacting a profound reconfiguration in the inner organization structure of the pharmaceutical industry. For, a special provision that amended the original IMI grant agreement allows the industry to sustain a large chunk of its operating costs (up to 30% in total, which can however reach the 100% for a single project) outside Europe. As an IMI representative explained:

*In our contract, it is clearly stated that only EU costs are eligible for funding. However, 2–3 years ago, on the basis of the dynamics… of the different conformation of the market of the industry… there was a board decision that allowed a special provision*

*according to which the industry can sustain up to 30% of the costs outside Europe. For a single project, that could even amount to 100%...*

Interview with IMI representative

Third, the creation of a unified scientific and technological landscape hinges on a further crucial aspect, the removal of entrenched competitive barriers among industries. Aside from creating closer connections between academia and the industry, IMI was indeed primarily geared to foster the establishment of collaborative relationships among industries themselves, overcoming a longstanding competitive culture that prevented different companies from sharing resources and data (in a way that led to cost–duplication and project overlapping) by carving out and enacting a '*pre–competitive space*' of collaboration. The latter notion is ubiquitous in IMI's parlance and projects, and refers to what Webster and Eriksson (2008) design as the realm of "basic innovation", i.e. a non–competitive domain of research at the early–stage of product development. As recalled by an IMI representative:

*For EFPIA, one of the first priorities that led to the establishment of the program was to optimize resources of all the companies conducting the same kind of research, to identify and address more rapidly and at a lower cost issues that everyone had (but everyone was working in its own corner, thus duplicating expenses), without competing in that specific domain. For instance, if we find out that a certain compound is toxic (or not)… this information if of interest for everyone. IMI was launched to ease the worries of the industry in sharing these kinds of data.*

Interview with IMI representative

## 6.5 The leading role of the industry in IMI's projects.

As what observed so far already makes clear, in IMI a central role is performed by the pharmaceutical industry, and programmatically so. As the former IMI chairman, Michel

Goldman, has observed: “A key difference between the IMI and other public–private initiatives in the health-care area is that IMI projects stem primarily from pharmaceutical companies.” (Goldman 2012) In particular, the leading role of industrial actors in IMI projects can be appraised from at least two different perspectives.

First, the agenda setting and topic definition is the industry’s prerogative. IMI projects take their inception from having a group of industries agreeing on a common area of research. Then, they elaborate a call and find suitable academic partners. Finally, once the consortium is assembled, the project receives IMI funding, and can thus start its operations. As an IMI project manager argued – and displaying, in so doing, a peculiar understanding of the notion of causality:

> *Under IMI and IMI2,* because *industry is giving half of the contribution, the topic idea is coming from industry… Generally, [the topic] is something on which the industry is already working on, and the proposal they put forward relates to that. It would be very difficult for them to commit to a totally new idea, the ideas have to come internally.*
>
> Interview with IMI project manager

As such, if IMI projects are meant to create a new, unified landscape for biomedical research in Europe, the industry is empowered to define the boundaries of such landscape, while the public funding provided by the European Commission takes the form of an overt subsidy to the industry’s RandD strategy.

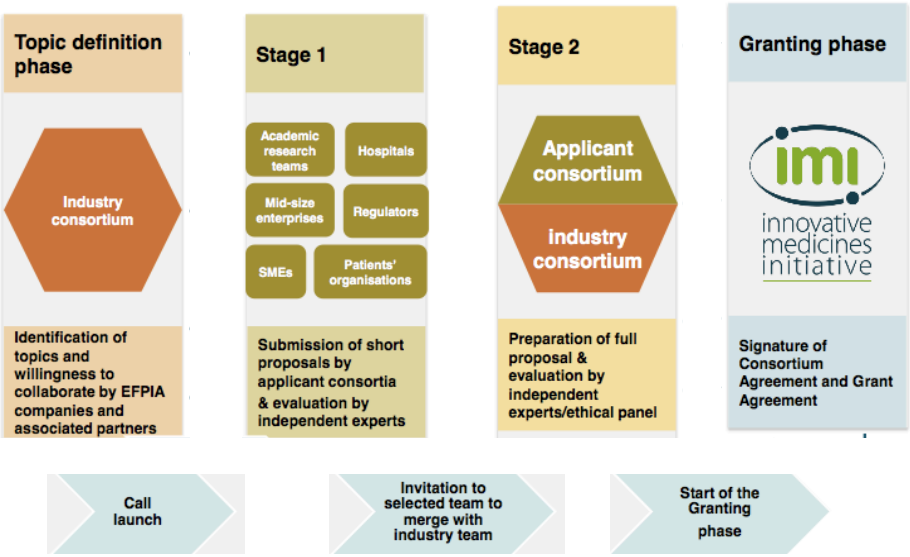



**Figure 17. IMI project: topic definition (source:IMI).**

Second, the pharmaceutical industry's contributions are 'in kind'. That is, rather than committing their financial resources, EFPIA members involved in IMI projects contribute to the overall budget by providing their own equipment, resources and staff time. This way, not only is the industry able to achieve significant financial savings. Most crucially, it is able to ensure that the process of knowledge–generation is geared towards industry–compatible standards. As observed by an IMI project manager:

> *The € 1 billion from EFPIA is in staff research effort, so they are not giving cash and do the academics do the work, but they are dedicating their own personnel. And this is a key point: we fund a collaborative project, and to have staff from pharma working on that project is really important, because of the cross-fertilization of ideas, and because results from the project can be immediately applied to the pharmaceutical industry.*
>
> Interview with IMI project manager

| **IMI: a new geography of European biomedical research:**<br>*From a fragmented research landscape ⇒ to a unified space of collaborative endeavor*<br>⇓ ⇓ ⇓ |
|---|
| **Step 1:** Reconfiguration of the identities, roles and functions of academia and industry:<br>*Industry: from product development ⇒ to knowledge generation*<br>*Academia: from knowledge generation ⇒ to product development* |
| **Step 2:** Framing of a 'European' pharmaceutical industry |
| **Step 3:** Creation and enactment of a 'pre–competitive space' of industrial collaboration |
| **Step 4:** Leading role performed by the pharmaceutical industry:<br>*(i) Agenda–setting and topic definition prerogatives*<br>*(ii) 'In kind' contributions ⇒ establishment of industry–compatible standards* |

**Table 3: Synopting overview of IMI's endeavor.**

The previous sections represent an overview of IMI that has become, since its inception, a mainstay of the European bioeconomic sector as well as an established tool in the EU science policy. In what follows, I investigate how this governance tool is brought to bear on iPSC research practice, through the establishment of the European Bank for induced Pluripotent Stem Cells.

## 6.6 The European Bank for induced Pluripotent Stem Cells.

EBiSC was launched, in February 2014, as one of the two flagship stem cell projects sponsored by IMI. EBiSC was created as a consortium, comprising 25 European organizations, ranging from academic research centers, to SMEs, to major pharmaceutical corporations. A leading role in the project is performed by Pfizer (in charge of the private side of the consortium), and by Roslin Cells, a small company specialized in iPSC manufacturing, that originated as a spin–off of Geron–funded Roslin Institute (the birthplace of Dolly the sheep) at Edinburgh University (Roslin Cells which is in charge of the *public* part of the consortium).

The overarching aim of the project is to establish a pan–European iPSC repository, manufacturing and distribution facility, with the goal of addressing the increasing demand by iPSC researchers and pharmaceutical companies for quality-controlled, disease-relevant iPSC lines, data and cell services. EBiSC's main facility, which undertakes expansion, quality control and characterization of cell lines, is led by Roslin Cells and is located at the Babraham Research Campus in Cambridge, UK. In charge of coordinating cell line distribution is the European Cell Culture Collection (ECACC) of Public Health England and the UK Department of Health. Fraunhofer IBMT in Saarbrücken, Germany, is instead a 'mirror site' in charge of providing comprehensive operational back up.

More in detail, the first objective of EBiSC is to establish a 'Foundational Collection' (henceforth: FC) of iPSC lines, which represents the core component of the EBiSC catalogue, to be then widely distributed to academic labs and pharmaceutical research centers in Europe. The FC comprises both already existent cell lines from EBiSC partner labs (such as, most notably, the large iPSC library established at the Sanger Institute), and new lines that are generated by partners in EBiSC using funding resources in response to demand from project partners or third parties.

At first, EBiSC was conceived as a € 70 million project, that would have had to last 6 years, with the aim of deriving around 10.000 iPSC lines. However, following reduction in funding to € 35 million by IMI, project–duration was shortened to 3 years, at the end of which EBiSC is meant to evolve into a not-for-profit iPSC bank. Interestingly, budget–reduction did not prevent the project from going through. As observed by an academic partner in the project:

> *What's going to happen is that we'll be able to collect lot less, it's a much smaller resource, which will come with a commercial entity at the end of the project, and will be part of Pfizer and Roslin Cells. And this has partly to do with the fact that commercial partners aim for short-term commercial benefits, rather than long-term collaborations, and part with the fact that IMI cut funding significantly. It was supposed to be a 6 years*

*project, 70 million, and now is 3 years, 35 million. Again, what's interesting is the difference in interaction. If such a reduction of funding happens with academic partners, they would say "we can't do this", and would revise the proposal, and say "this is what we can promise". Commercial partners are instead "ok, we'll try!", even though everyone knows it won't happen what they promise...*

Interview with EBiSC partner

## 6.7 "Having a structuring effect on Europe": constructing 'European' iPSC research.

As a flagship IMI project, EBiSC has been designed and implemented as "the missing infrastructure" in the European iPSC research landscape (interview with CEO, Roslin Cells). Borrowing language laden with economic connotations, EBiSC partners have described the initiative in terms of a "structural investment" in the whole iPSC sector in Europe (field notes 2015), one which is meant to establish the "whole supply chain" (field notes 2015) of iPSC research, from tissue sample procurement through appropriate consent from donors, to iPSCs derivation, expansion and distribution. As such, EBiSC is meant to accomplish a number of different objectives.

A first aim is to *establish connections* among the so far disjointed different steps of iPSC research, and *synergies* among the various institutions at different stages involved in it.

A second important objective is to create a *unified space* and a *marketplace* for European iPSC research through a governance–by–standards approach (Webster and Eriksson 2008). A defining characteristic of the initiative is indeed the strong focus on *standardization* – in order to address a twofold shortcoming in current iPSC research practice, the *heterogeneity* in both iPSC culture conditions and consenting practices, which in turn allows the distribution of high–quality, well–characterized and commercializable cell lines. To this end, EBiSC set out to homogenize reprogramming methods and culture

conditions among the partner labs, as well as to establish a single informed consent form, that could guarantee the widespread circulation of cell lines. As argued by the CEO of Roslin Cells:

> *At the moment, the problem is not making iPSC, it is the procurement. The delays are upstream. You do the collaboration, you work on the cell lines, get some nice things, then go out to the OTT, and you discover that the initial consent is not in line with the commercialization! That's why pharma in EBiSC is very interested in standardizing the upstream part.*
>
> Interview with CEO, Roslin Cells

The rationale of the project is, thus, twofold. First, to agree on common standards among all partner labs, which represent some leading iPSC research centers at EU level. Second, to adopt a 'trickle–down' approach to standardization, facilitating the diffusion of the standards being adopted in EBiSC to the rest of the iPSC research field on the continent, that which could lead to the standardization of the entire field. As explained by EBiSC's project leader:

> "*The iPSC field is still in transition. But I think that the IMI scheme of funding allows us to change that whole landscape… What we are doing is to create a large infrastructure that in itself will engage with a number of different partners across Europe, and therefore facilitate the building of consensus. The consensus will then lead to the standardization. […] And also, it's a degree of normalization of the product, that at this phase it helps to grow and validate the market."*
>
> Interview with EBiSC Project Leader

Finally, consistent with the leading role of the industry in IMI projects, industrial actors are seen as 'natural' beneficiaries of EBiSC (field notes 2015). First, through EBiSC, the industry can reach out to academia and "understand how to use the technology" (interview

with representative from Roslin Cells). Second, the establishment of a large repository of iPSC lines can facilitate the pharmaceutical companies' access to a greater amount of standardized and commercializable cell lines. Furthermore, public funding made available by the EU commission performs the crucial function of taming risk for the companies involved in the project, while also facilitating their capacity–building process. As explained by a Roslin Cells' representative:

> *EBiSC is tremendously important to us, because it's a grant-funded activity so it's the best also if you are losing money. What it allows our company to do is to achieve scale, which is a key competitive advantage over other companies.*
>
> Interview with representative of Roslin Cells

## 6.8 Conclusions.

In the European Union, amid profound and largely unresolved difficulties that define the contours of a critical challenge for its political identity, the life sciences and biotechnology, in reason of the innovation potential they entail, are increasingly being recruited to frame the basic elements of the supranational order–in–the–making. Major initiatives in science policy, such as IMI, are thus bound to provide the resources through which an important component of the European political identity is negotiated and constructed.

Specifically, in this chapter I have analyzed how the commitment advanced by EBiSC – as a flagship project established within the IMI framework – to create close linkages amongst public and private actors is encoded and materialized in its efforts at operating a thorough standardization of iPSC research practices, ranging from donors' consenting procedures to reprogramming methods and cell culture conditions. Articulating a translational vision that revolves around the blurring of institutional boundaries and the reconfiguration of the roles and functions performed by the industry and academia – with

the former geared to become a site of knowledge–production, and the latter a producer of innovation – EBiSC set out to standardize the field of iPSC research at the European level, so as to enable the seamless flow of knowledge between the academic and industrial research centers.

In light of these features, the development of European iPSC research has taken a markedly different path from its American counterpart. Expounding these differences is aim of the following, concluding chapter of this dissertation.

# Conclusions

This work set out, in chapter 1, by sketching the contours of the translational turn in biomedicine, and the ever–increasing importance being attributed, in biomedical as well as policy circles, to the acceleration of biomedical innovation. In this respect, the derivation of iPSCs by Japanese scientist Shinya Yamanaka in 2006 was hailed as a paradigm changer, one that not only rewrote chapters in biology textbooks, but also led to the swift adoption of iPSC–based technologies for widespread translational efforts.

Against this background, this dissertation has thus taken a comparative approach to analyze the emergence and consolidation of iPSCs as translational devices by juxtaposing three leading iPSC research organizations, NYSCF, HSCI, and EBiSC, operating in two different political contexts, the US and the EU. Probing these platforms as simultaneous sites of innovation across science and governance, I traced the key junctures of their developmental trajectories, highlighting how the manipulations of cell fate and the governance arrangements at the heart of the three platforms established a catalysis of mutual reprogramming that yielded three distinct models of socio-technical innovation around stem cells.

In these concluding remarks, I would now like to go through the main themes that have emerged in the course of the dissertation, and expand some of the lines of analysis that have been left implicit in the empirical analysis of my case studies.

In this work I have drawn from the notion of biomedical platforms (Keating and Cambrosio 2003), focusing in particular on the *hybrid performativity* of normative and epistemic practices that characterize their endeavors (see chapter 3). Deploying this notion within a co-productionist framework (Jasanoff 2004), I uncovered two distinct ways of

applying the co–productionist lenses to the study of biomedical platforms: what I have termed the *endogenous* and *exogenous* forms of co–production (see also Marelli and Testa forthcoming).

Harnessing this methodological toolkit for the analysis of my case studies, I probed, first, how the three platforms enact three distinct models of iPSC-based innovation, through the endogenous co-production of mutually reinforcing governance and epistemic standards, whereby: (i) divergent normative visions become crystallized in equally distinct governance and organizational structures; and (ii) the standardization practices for taming the unruliness of human pluripotency encode and reinforce these different institutional orders. Specifically, my analysis led to the following findings.

For one thing, NYSCF and HSCI were revealing case studies of the multi–faceted imaginary revolving around clinical translation in the US, and the different approaches to translational iPSC research emerging within the very same political context. Both NYSCF and HSCI set out from a common twofold objective: the creation of institutional structures that could insulate stem cell research from unwarranted political interferences, while enacting modes of scientific investigation and epistemic practices that could accelerate the translation of stem cell–based discoveries to the clinic. The scope and outcomes of their endeavors, however, differed remarkably one from the other.

As expounded in chapter 4, NYSCF has programmatically strived to challenge established experimental practices in the stem cell field, accruing agency within the organization in order to catalyze a change in paradigm of Kuhnian revolutionary salience. To this end, it adopted a venture philanthropy model of governance, one that borrows concept and practices from the disruptive innovation approach of Wall Street financiers and New York City venture capitalists, and one that is geared to the pursuit of "high–risk, high–return projects" that would normally not receive funding or attention by risk–adverse funding and research institutions. The creation of the first fully automated robotic system for iPSC derivation, expansion and differentiation – a project deemed by NYSCF's

investigators themselves as being "so high risk that it is not known whether it is going to be rewarding" – best epitomizes the all–out translational thrust of this organization.

Probing the entrenchment of stem cell research at a bastion of American academic research, Harvard University, chapter 5 focused on the establishment of the Harvard Stem Cell Institute and the iPS Core facility. Differently from NYSCF, HSCI advances a translational research agenda that is geared to sustain established research practices in the field of stem cell research. It also upholds the agenda–setting prerogatives of Harvard's stem cell community through the construction and fortification, against President Bush siege on stem cell research, of a self–governing citadel of science insulated from the underlying socio-political context, thus re-enacting the cherished post-world war II model of science governance, that frames scientific autonomy as a fundamental principle for the effective translation of scientific advances into societal benefits. In parallel, HSCI has aimed to "strike the right balance" between 'basic' and 'applied' stem cell research, that which required, along with the implementation of explicitly translational programs, preliminary significant investments in basic science.

Moving to the European context, chapter 6 analyzed how the commitment advanced by EBiSC – as a flagship project established within the IMI framework, the largest public–private partnership in the life sciences – to create close linkages among public and private actors is encoded and materialized in its efforts at operating a thorough standardization of iPSC research practices, ranging from donors' consenting procedures to reprogramming methods and cell culture conditions. Articulating a translational vision that revolves around the blurring of institutional boundaries and the reconfiguration of the roles and functions performed by the industry and academia – with the former geared to become a site of knowledge–production, and the latter a producer of innovation – EBiSC set out to standardize the field of iPSC research at the European level, so as to enable the seamless flow of knowledge between academic and industrial research centers.

Against this backdrop, table 1 provides a comparative overview of the main governance and epistemic arrangements of the three organizations analyzed in this work.

| | NYSCF | HSCI | EBiSC |
|---|---|---|---|
| Institutional setting | Non-profit/Venture philanthropy | Academic (US-style) | Public–Private Partnership (PPP) |
| Imaginary and model of innovation | Disruptive innovation<br><br>(centralization) | Sustaining innovation<br><br>(customization) | Standardization of EU research landscape (standardization) |
| Organizational structure | Translational hub (centralization of agency) | Virtual network (distribution of agency) | PPP (reconfiguration of agency) |
| Governance and Steering | Venture philanthropy | Harvard Faculty | European Commission and EFPIA |
| Propensity to epistemic and financial risk in advancing translation | High | Low | Medium to high (due to risk mitigation ensured by public funding) |
| Standardization technologies | Global Stem Cell Array (disruptive automation) | iPS Core Facility (trained craftmanship) | Partner labs (governance–by–standards) |

**Table 4. Synoptic overview of NYSCF, HSCI and EBiSC models of iPSC–based innovation.**

Other than accounting for a platform's endogenous dynamics, the methodological toolkit developed in this dissertation is further conducive to bring into relief the dynamics occurring at the platform–context interface, thus probing the *exogenous co–production* of scientific and normative orders at a higher scale of political significance. In conclusion, I would thus like to bring to the fore and address two sets of questions typically neglected by the scholarship on platforms, namely: (i) how do pre–existing socio–economic–political regimes affect the platforms' own innovation dynamics? (ii) What are the *normative* implications for the socio–political *macro*–order that are raised by the platforms'

endeavors? In other words, what is the 'reprogramming' role that platforms perform on their broader context?

Notwithstanding the irreducible performativity that characterizes each single platform (see chapter 3), the configuration of the political landscape in which platforms are situated greatly affects their innovation dynamics. This aspect becomes patent by juxtaposing the political developments in the US and the EU.

In the US, the federal funding ban enacted by President Bush in August 2001 has led to the development of stem cell research in a sort of political vacuum, which was conducive to the establishment of privatized regimes of stem cell innovation. For, constituencies not accustomed to be science policy leaders, namely individual states and organizations (Thompson 2013), strived to "take up the slack" that the federal government was leaving (Cook 2004) through bottom–up initiatives largely devoid of any coordination with governmental agencies such as the NIH. In turn, this triggered significant experimentation in science policy: those empty spaces opened up by the retreat of the federal government from a key area of biomedical innovation had to be filled by innovative and more flexible regimes of governance (Nowotny and Testa 2011), advanced by new biomedical collectives tinkering with new norms, standards and forms of regulation. Notably, this policy configuration further led to the rise of endeavors, such as NYSCF's, geared to open up the field of stem cell research through the introduction and dissemination of new standards, protocols and experimental practices.

The development of European stem cell research, on the contrary, has proceeded through a marked top–down approach, in which institutional actors such as the European Commission, as well as established organizations traditionally involved in biomedical research, such as major pharmaceutical corporations, have maintained a strong performative function, steering the evolution of the entire field. The European dimension takes on further significance insofar as it imbues stem cell research with a distinctive

(supra)nation–building commitment, conspicuously absent from its American counterpart. Driven by the intent to construct an integrated biomedical research landscape at EU level, EBiSC is symmetrically aimed at advancing the innovation strategy of the EU, which is seen as a cornerstone of its process of political consolidation, and at creating a distinctively 'European iPSC research'. To this latter aim, EBiSC is thus meant to reach a closure on a set of common standards to be agreed by partners lab, and to be widely disseminated to the entire iPSC field.

| iPSC research | United States | European Union |
|---|---|---|
| Actors involved | New biomedical collectives | Institutional and established actors (European Commission, pharmaceutical corporations) |
| Approach | Bottom–up | Top–down |
| Aims of standardization practices | Opening–up the field | Reaching a closure |
| Sociotechnical imaginary | Privatized regimes of innovation | (Supra)nation–building commitment |

**Table 5. How differences in political regimes affect configuration of stem cell research in US and EU.**

As for the *normative implications* of the stem cell initiatives mapped in this dissertation, the two political contexts, again, present interesting differences.

In the US, the federal funding ban contributed to the articulation of a specific form of *neoliberal* biopolitics, in which definitions and potential uses of life were no longer the exclusive prerogative of the US government and federal legislation, but were partially left to the forces of a market composed of entrepreneurs, philanthropists, scientists, and medical doctors (Thompson 2013).

The neoliberal character of initiatives such as NYSCF lends itself to analytic scrutiny in at least a twofold respect. First, vis–à–vis the retreat of the federal government from the field of stem cell research, the devolution of the agenda–setting prerogatives to an active array of wealthy philanthropists and patients advocates had the effect of redrawing (or

gerrymandering) the boundaries of the polity having jurisdiction over stem cell research policy, empowering a subpopulation of stakeholders (who became the *de iure* public for stem cell research) and turning them in proxies for the public good in place of the general public. In spite of the *universalistic claims* they advance, these initiatives maintain in fact a marked *privatistic stance* (for, Thompson (2013) notes, patients advocates do not intend to speak for everybody). Accordingly, Benjamin (2013) argues, the power of forms of claim–making based on *biological citizenship* (Rose and Novas 2005) – which is centered around a biological conception of a shared identity and which represents a hallmark of contemporary neoliberal subjectivity – increasingly tended to displace *social* and *political* citizenship claims, based on "interest–group politics" (concerned, for instance, with social justice issues), and the expression of substantive normative views by means of the (allegedly regular, albeit contested) electoral process which lead to the election of President Bush.

Second, insofar as "biological citizenship claims presume an autonomous individual working on his or her body in a more or less private arena free of state regulation" (Benjamin 2013), they actively supports a framing of stem cell research as a 'personal health' issue, as opposed to a 'public health' issue. In so doing, such claims advance an "upwardly tilted public agenda" (Sckopcol 2004, quoted in Benjamin 2013) rooted in a neoliberal and consumerist stance concerned more with promoting the market availability and expansion of innovative stem cell technologies, than with guaranteeing fair and shared access to the future proceeds of innovation. As noted by Benjamin (2013):

> *Stem cell advocates are concerned with expanding and protecting a consumer–based liberalism, ensuring access to future biomedical goods and services, and in that way they are very similar to other public interest and citizen advocacy groups that have been ascendant for some time. In one study of this trend, scholars describe a "postmaterialist" liberalism thriving in the civic sphere, increasingly focused on issues*

*that appeal to their middle–class supporters, which "have become less likely over time to ally with traditional liberal groups on behalf of re–distributive social programs".*

From a science policy perspective, initiatives such as NYSCF's, based on a venture philanthropy model of governance, entail an important conceptual change, that sets them apart from established models of science steering and governance. For, philanthropy–based governance actively seeks to grant private philanthropists exclusive access to science's "control room", something that not even the "new social contract for science" (Jasanoff 2005) - aimed at forging closer ties between academia and industry, from the 1980s onwards - had envisaged to such depth. Whereas in fact in this latter model the scientific agenda, while exposed to the influence of private capital, was still at least in principle subjected to public scrutiny and oriented towards the production of social goods (Guston 2000) - however polluted in practice by continuingly arising conflicts of interest the goal may be (Mirowski 2011) - in the venture philanthropy model the agenda-setting prerogatives are programmatically devolved to private philanthropists, who, in times of austerity and reduced public budgets, are able to play an "outsized role in who withers and who grows" (Bradach and Kim 2012, quoted in Grossman et al. 2013) by redistributing excess capital accumulation to targeted projects, designed to carry out their vision, without a public mandate and with little oversight as to the programs supported.

Far from being an isolated case confined to NYSCF, the spread of (venture) philanthropic science across the whole spectrum of scientific disciplines in the United States is relevant, and has a significant impact in re-orienting research priorities, the deployment of material and cognitive resources, as well as the very role of science in society (Nature 2008; Krimsky 2011; Barkan 2011; Broad 2014). As a March 2014 New York Times article - aptly titled *Billionaires With Big Ideas Are Privatizing American Science* - framed the issue, "American science, long a source of national power and pride, is increasingly becoming a private enterprise, becoming shaped less by national priorities

or by peer-review groups and more by the particular preferences of individuals with huge amounts of money" (Broad 2014).

In the European Union, amid profound and largely unresolved difficulties that define the contours of a critical challenge for its political identity, the life sciences and biotechnology, in reason of the innovation potential they entail, are increasingly being recruited to frame the basic elements of the supranational order–in–the–making. Major initiatives in science policy, such as IMI, are thus bound to provide the resources through which an important component of the European political identity is negotiated and constructed. In that regard, aimed primarily at tracing a new geography of European biomedical research, IMI set out to create a "unified space" (field notes 2015) of science and technology at the European level through the coupling of public and private actors. In so doing, rather than attributing equal agenda–setting priorities to the different actors involved, IMI programmatically devolves to EFPIA–associated companies a leading role in the steering of its projects, thus empowering the industry to define the boundaries of the integrated research landscape that it strives to construct.

Therefore, in conclusion it should be noted how, in spite of their differences, the American and European initiatives mapped in this dissertation nonetheless maintain a common feature, upholding a bioconstitutional framing of the position of science within the polity (Jasanoff 2005; Jasanoff 2011) that sideskirts the stream of recent efforts aimed at 'opening up' science substantively to public engagement (see, e.g., Nowotny, Scott, Gibbons 2001, Prainsack 2011).

# Appendix I – Methodological note

This thesis is based on analysis of published materials (scientific, policy, regulatory documents, journal articles, and videos) as well as on ethnographic fieldwork, which started at HSCI in October 2013, at NYSCF in April 2014, and at EBiSC in September 2014. Fieldwork has consisted in multiple visits to the two facilities, attendance to a number of closed-door meetings (between scientists, clinicians, and representatives from multinational pharmaceutical companies, instruments manufacturers, software developers, and others), access to confidential documents, and semi-structured interviews with relevant stakeholders, ranging from graduate students to the CEO and executive director of the organizations (a complete list follows). All but two of the interviews were recorded, transcribed, and coded. All interviewees gave verbal consent to be interviewed. Some of them required that their statements be anonymized.

**List of semi-structured interviews:**

**Harvard:**

October 3, 2013; April 3, 2014; April 7, 2014; May 28, 2014, Cambridge (MA), Leader of iPS Core Facility, HSCI

October 2013-November 2014 (multiple interviews, n>10), Cambridge (MA) Head of iPS Core Facility, HSCI

October 22, 2013, Cambridge (MA), (former) Head, Genome Editing Service, iPS Core Facility, HSCI

October 24, 2013, Cambridge (MA), (former) FHS Project Manager, iPS Core Facility, HSCI

November 6, 2013, Cambridge (MA), Lab Manager, Kevin Eggan Lab

February 2, 2014, Cambridge (MA), Regulatory Affairs Manager, iPS Core Facility, HSCI

April 22, 2014, Cambridge (MA), Research Assistant, iPS Core Facility, HSCI

July 23, 2014, Cambridge (MA), Executive Director, HSCI

August 7, 2014, Boston (MA), Biomedical Science Liaison, Eagle-i, Harvard Catalyst

August 7, 2014, Cambridge (MA), Executive Director, HSCRB

October 2, 2014, Skype interview, Director, HSCI

**Other relevant stakeholders involved in iPS Core Facility projects:**

November 8, 2013, Skype interview, Director of Marketing and Sales, bio–imaging company

April 8, 2014, Cambridge (MA), manager and representatives from Japanese corporation

May 7, 2014, Telephone interview, Head of Stem Cell Program, pharmaceutical corporation

May 9, 2014, Cambridge (MA), Research Coordinator/Genetic Counselor, Boston Children's Hospital

**NYSCF:**

April 10, 2014; May 22, 2014, New York City (NY) and Skype interview, Scientific Programs Director, NYSCF

April 10, 2014, New York City (NY), Principal Investigator, NYSCF

April 10, 2014, New York City (NY), Automation Systems and Stem Cell Biology Director, NYSCF

April 10, 2014, New York City (NY), Staff Scientist, NYSCF

April 10, 2014, New York City (NY), Senior Systems Architect, NYSCF

April 10, 2014, New York City (NY), lab manager, NYSCF

April 10, 2014, New York City (NY), Human Subjects Research Coordinator, NYSCF

July 24, 2014, Skype interview, Helmsley Investigator, NYSCF

July 30, 2014, Skype interview, CEO, NYSCF

November 21, 2014, Skype Interview, SCRO Committee Chair, NYSCF

February 12, 2015, Skype Interview, Chief of Staff, NYSCF

**iPS Core Facilities affiliated to the COREdinates consortium:**

April 17, 2014, Boston (MA), Principal Investigator, hESC Core Facility, Boston Children's Hospital

July 15, 2014, Skype Interview, Director, iPSC Core Facility, Penn Institute for Regenerative Medicine, University of Pennsylvania, PA

July 18, 2014, Skype interview, Manager, SKI Stem Cell Research Facility, Memorial Sloan Kettering Cancer Center, NY

July 26, 2014, Skype interview, Director, iPSC/hESC Shared Resource Facility, Mount Sinai School of Medicine, NY

**Cellular Dynamics International:**

October 2, 2014; November 28, 2014, Telephone interviews, Vice President of Research and Development, Manufacturing and Quality Systems and Chief Operating Officer, CDI

November 26, 2014, Telephone interview, Vice President and Chief Commercial Officer, CDI

**EBiSC/IMI/EU:**

September 26, 2014, Milan (Italy), Director, Center for Ethics and Law in the Life Sciences (CELLS), University of Hannover

December 5, 2014, Brussels (Belgium), Principal Scientific Officer, DG Research and Innovation, European Commission

December 8, 2014, Brussels (Belgium), Scientific Project Manager, IMI

February 17, 2015, Brussels (Belgium), Legal Officer, IMI

February 17, 2015, Brussels (Belgium), EBiSC Project Manager, IMI

April 28, 2015, Edinburgh (United Kingdom), CEO, Roslin Cells Ltd.

April 28, 2015, Edinburgh (United Kingdom), Head of Development Oprations, Roslin Cells

April 28, 2015, Edinburgh (United Kingdom), Business Development Manager, Roslin Cells

April 29, 2015, Potters Bar (United Kingdom), Director, UK Stem Cell Bank

**Closed–doors meetings attended at Harvard:**

Automation Project meetings: October 21, 2013 (Technical and General meeting); January 8, 2014 (Technical and General meeting); April 7, 2014 (Technical and General meeting); August 5, 2014 (Technical and General meeting); October 31, 2014 (General meeting)

Pharmaceutical Company Project meetings: November 15, 2013; April 16, 2014

FHS Project standardization meeting: January 15, 2014

Protocol standardization meeting: December 18, 2013

Kevin Eggan Lab meetings: from October to December 2013

**IMI/EBiSC/EU meetings:**

EBiSC Ethics Advisory Board, Hannover, February 19, 2015

**Other case studies-specific stem cell conferences attended:**

May 8, 2014, The Next Gen Stem Cell Annual Conference (Stem Cell Core Facilities Session), Saratoga Springs (NY)

October 22-23, The New York Stem Cell Foundation Annual Translational Conference, New York City (NY)

**Internship in Giuseppe Testa Lab at the European Institute of Oncology (IEO):**

May 2013 - August 2014: attendance to weekly group meetings and practical involvement in laboratory activities

September 2014 - ongoing: attendance to weekly group meetings

**Other relevant (but not case-studies related) interviews:**

May 5, 2015, Sheffield (United Kingdom), Stem Cell Scientist, Sheffield University

May 12, 2015, Milan (Italy), Director, Drug Discovery Unit, European Institute of Oncology (IEO)

**Other relevant (but not case-studies related) meetings attended:**

February 18, 2015, EuroStemCell Meeting, Brussels (Belgium)

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