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Systems Bioethics and Stem Cell Biology

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Abstract The complexities of modern science are not adequately reflected in many bioethical discussions. This is especially problematic in highly contested cases where there is significant pressure to generate clinical applications fast, as in stem cell research. In those cases a more integrated approach to bioethics, which we call *systems bioethics*, can provide a useful framework to address ethical and policy issues. Much as systems biology brings together different experimental and methodological approaches in an integrative way, systems bioethics integrates aspects of the history and philosophy of science, social and political theory, and normative analysis with the science in question. In this paper we outline how a careful analysis of the science of stem cell research can help to refocus the discussions related to the clinical applications of stem cells. We show how inaccurate or inadequate scientific assumptions help to create a set of unrealistic expectations and badly inform ethical deliberations and policy development. Systems bioethics offers resources for moving beyond the current impasse.

Keywords Bioethics · Developmental biology · Embryo research · History · Systems biology

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Prologue

Our best scientific knowledge ought to inform the ethical deliberations of those whose chosen profession is to attend to values in the life sciences and medicine. That is, it should matter to bioethicists to get the science right. Though ethical prescriptions should not be 'read off' from the science (what *ought* to be ought not to come from what *is*), neither should ethical deliberation be undertaken in ignorance of our best available scientific knowledge.

To say that bioethicists do not much pay attention to science, despite pronouncing on its permissibility or impermissibility, is not to say something particularly novel. But when scientists make this sort of accusation, sometimes they present an image of science according to which 'our best scientific knowledge' is of a piece and infallible. That is an unacceptable image of science. A more apt image envisions scientific concepts, norms, theories, and results as contextualized and contingent, as shaped by many factors, as contestable and contested (at least *within* the sciences), and as generating partial approximations to reality.

Historians and philosophers of science (especially those well-versed in the science in question) as well as scientists (especially those who reflect about the ways scientific knowledge is generated) can be trustworthy partners to bioethicists seeking to engage more deeply and more adequately in informed evaluation of science and medicine. Together, such interdisciplinary collaborators can shed new light on normative issues, uncover poorly justified assumptions, and promote constructive

discussion and debate about controversial topics. In this article, we demonstrate just how.

We begin with an increasingly common scenario faced by bioethicists: Disagreement among scientists, clinicians, and regulators about how to proceed with the clinical application of a 'hot' field of scientific research, in our case stem cell research. We urge that resolving such disagreements will benefit from a new approach to bioethical inquiry. After briefly introducing elements of such an approach, labeled *systems bioethics* by one of us (JSR), we suggest how a systems bioethics framing of questions about how to conceive of stem cells in the context of clinically driven basic and applied research can open new avenues of inquiry and dialogue. In particular, we emphasize how scientists, clinicians, and systems bioethicists can and should inform sound stem cell science and sound stem cell policy. We focus on stem cells as our core case because stem cell science and clinical hopes raise special questions, and so call for special responses.

In a recent article in the *New York Times*, science writer Nicholas Wade captures a core debate about the prospects for stem cell use [52]. Focusing on mouse experiments from 2001, Wade reports that bone marrow (with its presumed stem cells) generated heart cells in mice and that "researchers held out the hope that the procedures could be applied to people, too." Four years later, several clinical trials have shown limited success. "[C]linicians say they are encouraged, [but] researchers are considerably more skeptical." Stanford's Irving Weissman is quoted as saying that "these [clinical] studies are premature and may in fact place a group of sick patients at risk," basing his assessment in part on his own inability to replicate the results in mice. Yet, as Wade observes, "Clinicians have paid little heed to this apparent setback, arguing that there is an urgent need to try anything that is safe and might do good, regardless of whether its mechanism of action is fully understood." To this end, Wade quotes Emerson Perin of the Texas Heart Institute: "The basic-science guys don't see patients that are going to die, but I have to look them in the face every day... It's ludicrous to say we must understand the molecular mechanisms before we can try anything' [52].

This exchange gets at the heart of scientific and bioethical debates about how and when research should move into clinical trials. Additionally, and more specifically, the story gets at how the case of stem cell research is different from any other decision about when and how to take research from the bench to the bedside. We offer three conclusions, to be justified below:

1. that this decision is not for the basic research scientists to make, despite their claims to being the relevant experts with respect to benchside decisions; this is because their perspective is limited by the experimental system with which they work, and because their goal of understanding developmental processes does not always dovetail with more clinical considerations;
2. that this decision is not for the clinicians to make, despite their claims to being the relevant experts with respect to bedside decisions; this is because clinicians have a limited perspective that is fraught with clinical uncertainty, too infrequently informed by relevant basic science, and generally out of tune with the complexity of the developmental processes involved;
3. that stem cells represent a special case that, though like other controversial biological research (e.g., gene therapy) in critical respects, is importantly different in other ways; this is because stem cells, as such, are cultivated precisely to change, to develop in response to a changed environment, and therefore must be intrinsically dynamic and potentially unpredictable in some ways that may influence our decisions about the potential risks and benefits of applications.

Together, we argue, these considerations support the need for a new systems approach to bioethics.

In particular, the special developmental nature of stem cells best illustrates the need for a more intense and open dialogue between scientists, clinicians, and bioethicists. Progress in this regard within what we call *systems bioethics* acknowledges and builds on the complexities of the biological, medical, societal, and ethical questions in some of the same ways as the emerging field of systems biology brings together different scientific approaches from physics and chemistry to mathematics and computer science in order to better understand and intervene in complex biological systems.

We begin our analysis by unpacking a common depiction of stem cells: A mechanistic depiction that envisions stem cells as cars driving or being driven

along superhighways. In the next two sections, we argue that this sort of understanding badly informs scientific and clinical decision making. We then argue that an organic and dynamic systems approach that looks at stem cells in their actual environments is more appropriate, both to promote new avenues of inquiry and to inform better science policy.

The Scientists' Perspective

Stem cell scientists have played an extraordinary role in promoting the development and possible applications of their science. California's Proposition 71, passed by public referendum in November 2004, is a nice example. Many scientists lobbied heavily for Proposition 71 and its creation of the California Institute for Regenerative Medicine with $3 billion in public dollars. The organized resistance to Proposition 71 was comparably small, though a number of critics opposed the minimal governance structure afforded by the proposition [41]. The public debate, such as it was, appeared to be structured around two options: Either support the proposition and cure all diseases, or vote 'no' and condemn millions of Californians to an otherwise preventable death. The scientists argued, in a very traditional way though in a non-traditional context of scientific justification, that we need the science of stem cell biology as a public good, and they presented the research as if it were a matter simply of driving stem cells to work to cure all manner of diseases, from Parkinson's to AIDS.

This high-profile public effort, along with several recent announcements including the derivation of embryonic germ cells and male gametes from embryonic stem cells in mice, and the recent challenges to earlier observations regarding the effectiveness of bone marrow stem cells in improving cardiac function after a heart attack, have focused attention once again on the apparently rich capacities of embryonic stem cells and on the scientific community's interest in understanding and eventually controlling (some of) these capacities [3, 14, 21, 31].

Overly mechanistic thinking about the functioning of stem cells, however, misrepresents the best available understanding of development and may actually significantly impede progress towards this goal. Recent diagrammatic representations of stem cell differentiation portray stem cells as cars or other entities moving along roads and off ramps. Unfortunately, these mechanistic representations are inherently and instrumentally problematic, and they risk constraining our thinking about stem cells, both scientifically and politically, in misleading ways. In our view, more organic and holistic imagery is needed to liberate our thinking about stem cells. As the amount of stem cell research increases, and given the persistent mechanistic assumptions, it is all the more important to consider both the science and the various ways to understand it.

Helen Blau and colleagues give us a picture of stem cells as cars driving down a complex superhighway complete with off ramps, curves, and alternative routes [6] (Fig. 1).

Within this metaphoric framework, the focus, not surprisingly, is on how best to drive stem cells in the right way, at the right speed, making the correct turns and other maneuvers so that they arrive where and when their drivers intended. The underlying assumption appears to be that stem cells are mechanically defined and contained, and that the stem cell drivers are in charge.

Raewyn Seaberg and Derek van der Kooy have criticized this metaphorical model, calling for clearer definitions and more careful use of terms [42]. In particular, they have urged the research community to distinguish true stem cells from progenitor cells, though recent research suggests that this is not a neat distinction. They criticize the Blau et al. image for confusing different kinds of cells and offer what they call a 'tongue-in-cheek model' that stresses the straight-line, one-way path for stem cells, with a convenient roundabout for some cells to go in circles and replicate, while others roar ahead (Fig. 2).

Seaberg and van der Kooy's call for clearer definitions and careful use of terms is very important. Yet, their imagery (though tongue-in-cheek), still conveys the idea that genetic drivers determine whether the stem cells go in circles of renewal or move ahead. The road map may have changed, but the implication is still that stem cells are, in fact, already defined and mechanically tuned with engines and interconnected parts that can be driven in different patterns.

Gretchen Vogel effectively captures this mechanistic thinking common among many stem cell biologists as well as members of the wider public. She writes:

> In common parlance, they [stem cells] have been defined as cells that can both renew themselves

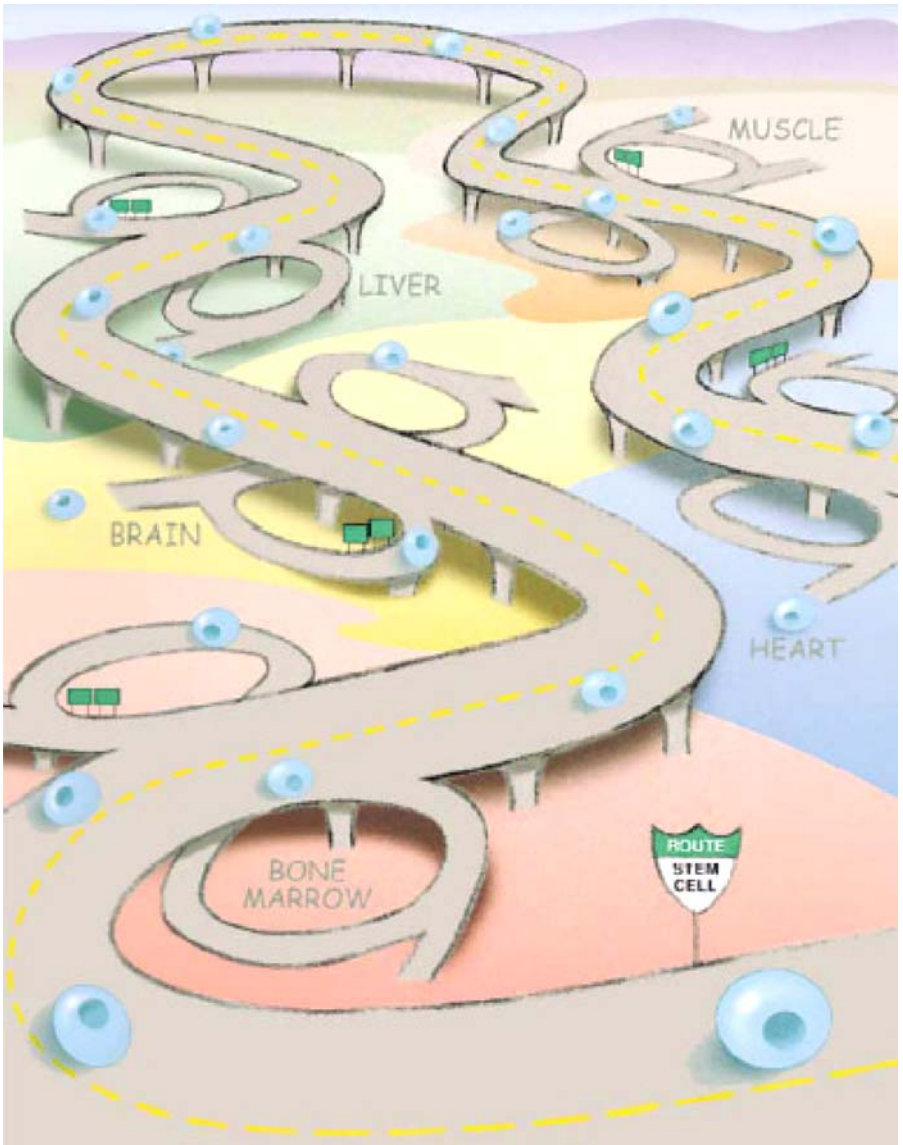

Figure 1 Reproduced with permission from Fig. 8 in ref. [6]: "The stem cell landscape depicted here illustrates the emerging characteristics of adult stem cells that include plasticity in cell fate, diversity of origin, and a multiplicity of tissue potentials. Stem cells (*blue*) are able to enter diverse tissue compartments from the blood stream (the stem cell highway) *via* 'on ramps' and generate appropriate cell types in response to homing signals or growth factors depicted on 'billboards'. In theory, all choices are reversible."

and give rise to more specialized daughter cells. But that is a functional definition, akin to saying that a car is a movable machine on four wheels. Scientists are keen to get under the hood and see which genes drive stem cells' engine of renewal. Although researchers have identified a few genes that seem to play a role, the key molecular switches remain a mystery [51].

Vogel's phrasing captures the idea that if we can work out the genetic and molecular mechanisms, we can drive stem cells to work, and this image 'drives' the research.

Such mechanistic emphases are problematic, however, insofar as they have misled (and may continue to mislead) researchers to see stem cells (and embryonic cells more generally) as more fixed than they actually are. In early human stem cell research we heard repeatedly that researchers were 'shocked' to discover that apparently differentiated cells can 'de-differentiate' or that cells have considerably more plasticity than had been assumed, especially by those researchers lured by genetic determinism. This reaction remains prevalent among biologists and especially within the wider research community who have been working with the assumption that there are genetic drivers

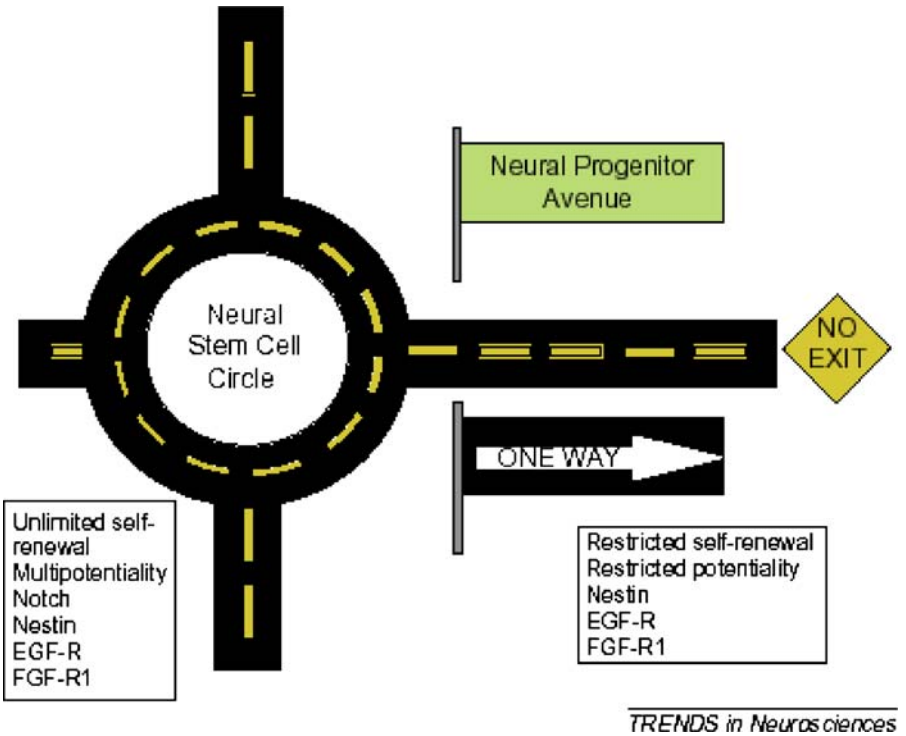

Figure 2 Reproduced with permission from Fig. 2 in ref. [42]: "A tongue-in-cheek model (with apologies to H. Blau) for neural stem and progenitor cells that emphasizes the empirically testable differences between stem and progenitor cells. The roundabout Neural Stem Cell Circle is a metaphor for the two cardinal properties of stem cells: the stem cell can self-renew (continue around the roundabout) and also asymmetrically generate neural progenitor cells that can differentiate into several different neural lineages (*streets*). For example, neural progenitor cells can exit from Neural Stem Cell Circle and proceed along Neural Progenitor Avenue, which is a one-way street that ends in a cul-de-sac (i.e., these cells are restricted in their ability to self-renew and in their options for differentiation). The *boxes* indicate functional properties and expression profiles for neural stem cells (*left*) and progenitor cells (*right*)."

controlling cellular cars, moving in one direction along pre-existing and confined highways. When faced with recalcitrant data, such as possible de-differentiation (U-turns), mechanistic metaphors invite mystical depictions of the putatively magical powers of stem cells: They can do things that no one has ever thought possible! Well, it is not true that no one has ever thought them possible, and we will all benefit from an understanding of stem cell biology that more nearly represents what actually happens during cellular development. To begin with mechanistic assumptions is to invite shock at what is to be expected from a more dynamic, organismal perspective.

Those scientists who publicly endorse a simplistic mechanistic metaphor (often by simplifying their own scientific understanding of the complexities of the biological system) are behaving unethically, because this particular way of simplifying the science suggests promises for therapeutic applications that we know to be extremely improbable. The best available developmental biology shows that we will not be able simply to drive stem cells to work. It will not be a matter of discovering simple mechanisms to culture stem cells *just so* in order to drive them the way we want. Development is more complex than that, and we value stem cells precisely because they are not simply mechanistically predetermined to become a particular type of cell – though this does not make them magical, either.

The Clinicians' Perspective

Clinicians do operate in a world where they have high incentives to make assumptions that it is possible to 'drive' stem cells, or any other functioning parts, to work for the desired end. They are rewarded for thinking in terms of the parts that can be fixed or replaced rather than the interactive whole system that cannot. Mechanical hearts and other parts, replacement

valves or transplanted organs, plastic parts for joints and as a template for cell growth: We have seen astonishing successes with interventionist therapies. It is entirely understandable that clinicians, and the public they serve, want to push forward on all fronts. The question, then, is what should it take to move science from the bench to the bedside in any particular case.

Success stories of bench-to-bedside translation are unfortunately rare [19]. Moreover, some types of research seem to raise new challenges. Stem cell research is a case in point. Human embryonic stem cell therapies do not exist yet, but the approach envisioned focused initially on culturing cells of a particular desired type and then placing them at the site where they were needed. Sick heart muscle would receive stem cells that produce heart muscle. Pancreatic cells that do not function would receive replacements to produce the insulin missing in diabetics. Neural cells would be injected to repair lost brain function. And so on. The original idea for stem cell therapies centered on this hope for replacement parts. The replacements might be individual cells, or perhaps organs or tissue that could assume their proper place in the patient and take up proper functioning. In our experience, this is the image most widely propagated by scientists [25], the image most of the public holds, and probably the image that drove so many Californians to the polls to spend their money on stem cell research.

Recently, the idea of cell replacement has been displaced in some clinical and research quarters; replacement is apparently difficult to achieve, and so stem cell researchers have begun to think more in terms of protection and mediated repair than direct replacement of cells or of function [48]. The idea here is to introduce stem cells to an injured area or an area of degenerative function based on the assumption that the stem cells will begin to stimulate the surrounding cells to function properly again – where 'properly' means carrying out the desired function [26]. This is a very function-driven picture, also evoking images of driving the system along the right road. However, in this case, the stem cells are not being driven to work themselves but are instead helping to drive the surrounding tissue to repair itself.

Unfortunately, the assumptions underlying this approach are also problematically dependent on overly simplistic views about just how deterministic cell interactions in development are and therefore about the likelihood of getting the stem cells to stimulate the 'proper' – and only the proper – function in neighboring cells. We will return to this central point about what is unusual about stem cell biology in the next section. For now, the question remains: What should it take to move stem cells from the bench to the bedside?

We would have to know that stem cells can be caused to develop as desired, generating (in one way or another) the right sort of thing. This means that we would have to first achieve these effects in cell cultures, in an artificial and highly controlled environment. In fact, stem cell cultures only exist artificially and we know little about any particular stem cells outside these cultures and how they will behave differently in each different environment and especially in more complex environments [37]. Here we come to the core point: Proponents of stem cell research are excited about stem cells precisely because stem cells are not fully determined, and because they respond to their changing environments. But this, by definition, also means that we cannot easily predict how they will behave in various environments.

The usual approach, and one well-studied in stem cell biology, is to try a proposed therapy, whether cellular, chemical, or mechanical, in an animal model such as a rat or mouse. Then, depending on the results, one option is to move to experiments with an animal more closely related to humans, such as a non-human primate model. But stem cells in different organisms are different, are located in a different environment, and are therefore a different 'system' altogether. Accordingly, another approach is to transplant human cells into an animal model used as an assay system. The resultant part-human chimeras might help to answer questions about the likely behavior of human stem cells upon transplant, but such chimeras are themselves a novel and different 'system', so inferences will not always be straightforward [37, 39].

What we can ask using these approaches is how stem cells behave and how likely they are to serve the therapeutic functions we seek. What we find, however, is accumulating information about stem cells in varied environments. We cannot know for sure how stem cells will behave in human systems. For example, to know how stem cells behave in one human is not to know how they will behave in another human, and to know how stem cells function in a healthy human is not to know how they function in a sick human. This is because it is precisely the variable potential of stem cells that makes

them exciting for researchers, and potentially therapeutic – or dangerous – for patients.

We suggest that clinicians will be unethical to turn too quickly to clinical experimentation, even in terminally ill patients, since there is a realistic chance that the plasticity of stem cells will cause them to behave pathologically upon transplantation. Among the diagnostic criteria for a cell's pluripotency is its ability to generate teratomas (tumors) with many cell types upon transplantation, so the possibility for harm in clinical stem cell transplant research is not negligible. Until further basic research has established the extent of the tumorigenicity associated with pluripotency – and how to regulate it – clinical research is premature at best.

We are not claiming that, in general, there is no amount of preclinical research that could adequately justify the transition to clinical studies in humans, but rather that, in stem cell research specifically, we have not conducted enough of the right sorts of studies to reduce the inferential gap between nonhuman animals and humans, and between nonhuman animal stem cells and human stem cells [37, 39].

Understanding Stem Cells Biologically

Mechanistic metaphors of genetic drivers in control of cellular cars miss the plasticity and vitality of stem cells, and the way that they interact within the external and internal environments that make up a complex system. Similarly, much of the ethical and political discussion about the ethics of stem cell research misses the complexity of both the scientific and the moral issues involved.

The nature of stem cells can be captured adequately only by appeal to more organic and dynamic images that better fit the reality of a highly interactive, regulative, and flexible embryonic development of the emerging system. And this is a particularly organic system. It is helpful here to revisit the original meaning of the term 'stem cell' introduced in 1896 by Edmund Beecher Wilson. Probably inspired by analogies with stem or root stock in plants, and aware that 'blasto' (from the term blastomere) meant 'stem', Wilson coined the term to identify cells that retain a complete complement of chromatin and have the capacity to give rise to either germ or somatic cells, and to distinguish them from other cells that had already become one or the other [54]. While his particular understanding of chromosomes has not stood the test of time in all respects, Wilson recognized the importance of growth and the capacity of individual cells for morphogenesis and differentiation, and he captured what is biological about stem cells. Stem cells have two characteristics: They are like the stems in plants, largely undifferentiated but proliferating cells; they are also capable of branching and specializing, responding to environmental conditions outside the cells, including nutrients, and other nearby cells (cf. [43]).

If we picture stem cells as similar to a growing plant or tree, we simultaneously capture the capacities, constraints, and context of these cells. We see a developing living system that has internal interactions of its own. We may be able to cultivate the stems, splicing together bits from different stocks or nurturing growth in one direction or another. But it is the internal structure, function, and interactions that ultimately determine the range of what is possible, whether the individual cells grow together within the intact blastocyst or are extracted from that blastocyst and are grown in culture.

From everything we know about stem cell biology, the environment in which the cells are grown very much matters [34, 37]. It is not a matter of genetics, let alone of self-contained genetic cars driving along on their own. Furthermore, attempts to use gene-expression patterns as defining signatures for stem cells raise more problems than they solve. Studies have shown a large diversity in expressed genes in different stem cells, thus rendering the search for a strictly genetic definition of 'stemness' virtually meaningless. ([20, 36]; see also [37]). Stem cells are therefore best characterized as responsive, regulatory systems that are very much interacting with and responding to their surroundings.

This alternative biological understanding of stem cells as regulated autonomous systems interacting with their environment is organic rather than mechanistic. It is not simply a matter of metaphoric representation, but actually central to the way we think about the science and its possible applications. Seeing stem cells as interactive and responsive systems rather than as preformed precursors to a specific set of possible end-products takes the interactive or epigenetic aspects of the developmental process into account. There is nothing mystical or vitalistic about this notion of stem cells as regulated autonomous systems. Quite the

opposite: Regulation, differentiation, and morphogenesis are strictly a consequence of the material interactions between the internal and external environments of stem cells and as such are amenable to scientific study and manipulation. But the emphasis here is on the epigenetic and not the preformistic aspects of development [29, 38].

Our proposed change of understanding from the mechanical to the organic should – but may not in itself – challenge the experimental practices of stem cell researchers. These practices follow their own logic in terms of what is technically feasible and they are continuously adapted to the challenges of experimental research. However, re-conceptualizing stem cells as biological agents will certainly affect our interpretations of empirical research results, our expectations for therapeutic applications, and our framework for understanding ethical and policy issues relating to stem cell research. Moreover, we hope this will help researchers and clinicians to recognize the true prospects and limits of stem cells in contexts – developmental, political, and social.

Another dynamic and organic attempt is Miguel Ramalho-Santos' proposal of a research program in stem cell biology based on the idea of stem cells as autopoietic entities [35]. His proposal is another example of how starting assumptions about what stem cells are, and how they function, change the 'search image' of researchers, thereby affecting both ongoing research as well as the interpretation of research results. The theory of autopoietic systems is one of several proposals in theoretical biology that focus on the properties of systems, or of organisms, as the primary explanatory framework for biological processes [30, 50]. Other related proposals emphasize the need to develop a formal approach to the question of the part/whole relationship in cells and organisms so as to adequately represent the role of internal as well as external environments, the importance of organizational relations, and the role and relevance of network properties and their consequences [23, 27, 45, 53].

Our organic understanding of stem cells incorporates several elements at the heart of these proposals:

1. Cells and organisms are the primary units of biological organization and integration. Both are spatio-temporal entities characterized by regulation and development. Because of their specific role in development and their regulatory properties, stem cells are part of both the cellular and the organismal level of organization (first- and second-order autopoiesis in Ramalho-Santos' terminology);
2. Regulation and differentiation are properties of dynamic systems (cells and organisms) interacting with their respective environments;
3. System properties, such as 'stemness', are relational properties that involve interactions with the relevant environmental contexts, and cannot be defined by their parts alone.

What all these proposals have in common is that they provide an interpretative context for experimental data. In that sense they contribute to the conceptual integration of biology, a role for theoretical biology that has regained prominence in the emerging context of systems biology [22, 23]. But these proposals also have practical consequences for empirical and theoretical research in developmental biology and for therapeutics. Here we briefly sketch how an organic perspective on stem cells could affect theoretical work in developmental biology – as Ramalho-Santos has already discussed several examples of how empirical research can be affected [35].

The choice of image, and so of conceptual possibilities, is especially important for efforts to model stem cell behavior mathematically. Previous models have mostly relied on a population dynamic approach [16, 28] and modeled differentiation as a stochastic branching pattern [5]. These approaches have led to some valuable insights, and several useful models have been developed in the context of a dynamical systems analysis [13]. All these models focus primarily on cells as the objects of analysis, emphasizing different characteristics, such as the dynamics of a biochemical reaction network inside a cell, interactions between cells, cell division, and cell death. All these models interpret differentiation as the transition between different cell states. As such, these models are consistent with the metaphorical description of stem cells as cars driven down a (one-way) highway.

To account for recent empirical results in stem cell research, future mathematical models will have to examine the role of environmental effects as well as of spatial influences and organizational relations on stem cell fate and dynamics (i.e., the classical network properties of biological systems) [1, 47]. This can best

be accomplished in the context of models that take a top-down perspective. Applied to mathematical models of stem cell behavior such a perspective would imply that we aim to model the whole organism as a four-dimensional object in space and time and within this model to define stem cells relationally in terms of their spatial position, their environmental signals, and their internal configuration, thus incorporating the results of empirical research.

Such a relational characterization of stem cells within an organism would provide a dynamic criterion of 'stemness' as a system property rather than as a property that certain cells have as a consequence of their own individual history. One of the advantages of our approach is that it gives a more convincing interpretation of trans-determination and the reversal of cell fate than other accounts.

One immediate consequence of this new conceptual and theoretical framework for stem cell biology is that individual stem cells are no longer the exclusive focus of analysis. Rather, the overarching developing system, i.e., the organism-in-context, is the primary and relevant object of analysis that, in turn, determines the biological functions of its component parts, such as stem cells. Such a 'top-down' approach to the study of biological systems is also the basis of the newly emerging field of 'systems biology.' What all proposals for systems biology have in common is that they focus on the system, whether it is an organism, a cell, or any other biological system, as the primary locus of integration. This makes it possible (at least this is the hope and the promise of systems biology) to bring together different experimental and theoretical approaches.

We suggest that a similar emphasis on the integration of different perspectives is also needed if we want to make any meaningful progress in the ethical reflections and policy recommendations connected to these types of research.

A New Interactive, Organic *Systems Bioethics*

To review: On our account, reflecting the best currently available science, stem cells are no longer seen as isolated cars on a super-highway. Quite the opposite: The properties of cells – whether they are stem cells or not, whether they can transdifferentiate or not – are seen as a function of the system in its context. In the same way that the spatial and temporal context of an ant colony determines the behavior of individual ants, or the regulatory states in a developmental system change depending on their spatial location and developmental time, in our proposal cell properties, such as 'stemness', are understood to be a function of the organism-in-context [9, 12].

A biological perspective on stem cells should also lead us to question the underlying assumptions that lead to overly optimistic expectations on the part of stem cell research advocates. Increased emphasis on the interactive and contextual elements of the process of differentiation and morphogenesis calls for more caution about our abilities to 'drive the stem cells to work' by either reprogramming or de-differentiating stem cells in just the ways we want. Turning back the internal clock of differentiation does not mean that these cells can then be reapplied in a different context that we define. Of course, this does not mean that we should stop this kind of research and the search for therapeutic applications. It reminds us, however, that attention to the organic and regulatory properties of the differentiation process will give a more realistic interpretation of the relevant developmental processes and the possibility of future therapeutic applications [44]. Researchers may one day be able to shape development more than we currently imagine, but this will only be possible by *cultivating*, not driving, the biological forces.

So far, we have argued in favor of a systems approach within stem cell biology, to foster genuinely developmental research that may facilitate some of the clinical integration foreseen by advocates of stem cell research, but also to foster appropriate skepticism regarding the more extravagant promises of clinicians and scientists. We now show the benefits of integrating a systems biology approach into bioethics, and of adopting an interactive, interdisciplinary, intersectoral approach to bioethics as such – systems bioethics.

The relationship between systems biology and systems bioethics is metaphorical, but not merely so. Substantively, both systems bioethics and systems biology take seriously the limitations of an atomistic 'parts-list' approach to biology. The foundational phenomenon of biology is development, and development is irreducibly systemic, dynamic, and interactive. As we briefly illustrate below, conceiving stem cells in systems terms reframes the scientific, clinical, ethical and policy discourses. Moreover, there is no such

thing as a stand-alone gene or cell or embryo or biological system; similarly, there is no such thing as a stand-alone bioethical issue or a stand-alone bioethical analysis. Rather, the substance of bioethics is itself a web of interacting elements each of which must severally and jointly be brought under scrutiny from multiple perspectives. Additionally, as others have noted, bioethical analysis must itself be richly multi-disciplinary and even transdisciplinary; the disciplines invoked must extend well beyond the currently well-represented disciplines of philosophy, religious studies, and experimental and clinical medicine, to include (*inter alia*) the history and philosophy of biology and medicine, economics, political theory, and the social studies of science.

Systems bioethics begins by taking seriously a systems approach to biology. Systems biology, as noted above, refers to the study of complex interactions that comprise and constitute living entities. One argument for systems biology is that, to borrow the words of Eva Neumann-Held, "so far, biology can describe organisms down to the molecular level of genes. However, the interactions of genes with other, non-genetic components to form an organism is far from being understood. ... In the description of organisms (more generally: Of systems), biology still has to perform the integrative part" ([33]: 107). Such is the challenge for the successful translation of molecular data into improved health outcomes, via the sciences of organismal development.

Something similar may be said of bioethics: Bioethicists have conducted atomistic analyses of particular aspects of the ethics of genetics, genomics, and developmental biology, but have not attended to the system or the interactions between the parts. Moreover, the central bioethical questions derive from either the medical clinical applications or from philosophical traditions applied almost *a priori*. These disparate analyses may form part of the story, but they have yet to be integrated in any plausible way either with each other, the science, or the sociopolitical and institutional contexts in which bench-to-bedside decisions are made.

The arguments in this paper so far have relied on historical and philosophical analysis of key concepts in stem cell biology, and developmental biology more generally. Our aim has been to subject the science to critical analysis in an effort to improve the science and increase the likelihood that it will generate social benefits. The latter can never be guaranteed, but taking outcomes seriously may result in novel upstream research and development so as to facilitate achieving the outcomes in question. We contend that seeing stem cell development as a regulated interactive process of biological systems has important bioethical and policy implications. Development, through morphogenesis and differentiation, is an interactive process based on many cell–cell and cell-environment interactions. The environment in which the cell finds itself, as much as the cell itself, determines cell fate. This means that it does not make biological sense to attribute special status to any cell, such as stem cells, in isolation from its complex web of interactions. In particular, policies protecting stem cells as such make no sense. Nor do policies specifically protecting egg cells or even fertilized egg cells, which have few capacities by themselves. Reasonable stem cell policies must not ignore the developmental context of stem cell research.

Much of the literature on stem cells has focused on traditional issues in moral philosophy and bioethics. Standard issues include analysis of the moral status of the embryo, the (typically utilitarian) justification of 'killing' 'possible persons' to possibly help actual persons, the plausibility and moral propriety of the distinction between discarded 'spare' embryos and newly created ones, the sourcing of embryos from women (and from females of other species), the ethics of human cloning, and under what conditions it is permissible to enjoy the fruits of evil (see, *inter alia*, [4, 10, 15, 17, 40, 46], and the March 2005 supplement of *Reproductive Biomedicine Online* devoted to issues in assisted human reproduction and stem cell research). These are all important issues, and despite an enormous literature devoted to their analysis, these issues remain enormously controversial and no resolution is in sight.

This suggests that traditional bioethics is ill-prepared to interpret the complexity of stem cell biology, and of developmental or systems biology more broadly. Too much bioethics scholarship fails to appreciate the complexity of genetics, genomics, and development more broadly. Within biology at least, the focus has begun to shift to regulated, complex interactive biological systems. Bioethics must now integrate a systems approach to biology, and make the transition to systems bioethics.

The aim of systems bioethics is to make normative and conceptual analysis actually matter to clinical

practice and science policy. This is achieved through the collaborative interaction of methods from multiple fields of inquiry to achieve integration of key concepts relevant to a joint public and scientific discourse about biological research and practice. We begin with conceptual studies in the history and philosophy of biology to inform critical analysis of the relevant science, and then integrate perspectives from the social studies of science, science and technology policy, and political theory (*inter alia*), to afford new ways to frame, explore, understand, and alter moral dimensions of scientific research in a civil society.

Just as a systems approach within biology can inform scientific and clinical understanding, a systems bioethics approach both to stem cell biology, and also to the normative analysis of stem cells in society, can inform our ethical and political reasoning about stem cells. First, cells do not just translate into products as if they were little mechanistic predictable factories. Organisms emerge epigenetically from interactions on multiple scales; what is amazing about development, as Veronica van Heyningen has emphasized, "is not that it sometimes goes wrong, but that it ever succeeds" at all ([49]: 771). One of the grand accomplishments of the Human Genome Project was the disestablishment of genetic preformationism [38] – hence the impetus for systems biology in the first place.

Second, early *in vitro* embryos are not future persons in any reasonable sense – though they may be deeply morally valuable; an epigenetic or developmental approach reminds us that destroying an *in vitro* embryo is not destroying a future individual. However precious these entities may be, the potential of these biological systems is determined not atomistically, not absolutely, but rather relationally, within a biological (and social, and clinical) web of interactions. More simply, cells do not become people without considerable contributions from beyond the cell membrane. It is noteworthy that some Christian biologists and commentators derive the opposite lesson from a systems approach, inferring full personhood from the continuity of development ([2, 18]; but see [11]). Of course, the moral debate about personhood is not to be settled merely by appeal to science – but neither should it be settled in ignorance of the relevant biology. A systems approach to the science is an excellent starting point for more productive deliberation.

Third, beyond informing our ethical understanding, systems bioethics provides a way to think about all the scientific, clinical, ethical, and political issues together and interactively. This systems approach rules out of bounds such rhetorical ploys as false dichotomies – for instance, that the stem cell debate is about 'protecting embryos' *versus* 'developing therapies to save lives'. What is at stake, rather, is a vastly more dynamic and complex set of considerations, all of which occur in the gray area between the stark, but false, extremes. Some of these considerations are normative, involving thick moral descriptions of the potentially competing values at issue, grounded in (though not read off from) scientifically adequate conceptions of the research. Other considerations are political and pragmatic, involving questions about decision-making under conditions of scientific and moral uncertainty.

There are also scientific and clinical decisions to be made under the same conditions of uncertainty. Though we cannot elaborate here, suffice it to note that from the perspective of systems bioethics, scientific research decisions, like clinical research decisions, demand a form of public accountability. This requirement of accountability should be understood as the requirement to give a justifiable account of one's decision and one's reasons for that decision [8]. Such justifications are commonplace in clinical research; they are required in the context of Food and Drug Administration investigational new drug submissions and the submission of research protocols to institutional review boards. So too should they be required for scientific research more generally, as emphasized, for instance, in the recent National Academy of Sciences voluntary guidelines for research with human pluripotent stem cells [32]. (They are also required in Canada and the United Kingdom for the licensure or approval of stem cell research.) These public justifications might then serve to inform political and pragmatic decisions, which are to be made on the basis of appropriate process in a civil society. ([7, 24]; see also [39]).

Conclusion

Viewing stem cells in mechanistic terms is limited, limiting, and downright misleading for science, clinical integration, and policy development. Our analysis has

not striven to provide concrete advice about the ethics of stem cell research, the particular policies that ought to be adopted, or the specific protocols that ought to be undertaken. Rather, we have tried to highlight the wide range of perspectives that must be articulated, rearticulated, and integrated in order for morally and socially justifiable progress in stem cell science. This exercise in systems bioethics has brought together aspects of otherwise disparate, isolated analyses of stem cell research from the history and philosophy of biology, developmental biology, theoretical biology, preclinical biomedical research, and bioethics. Other important perspectives have been mentioned only briefly in this initial analysis, but these important domains include political theory, science and technology policy, and the social studies of science. Consider this, then, as a prolegomenon to an adequate bioethics.

The discovery of stem cells and the elucidation of their functions occurred, and continues to occur in many instances, in the course of basic research in developmental biology [29, 37, 39]. In the push to drive stem cells to work in the clinic, let us not forget that stem cell biology is fundamentally developmental, and that to understand stem cells requires fundamental understanding of development [44]. Understanding how developmental processes work, and what role stem cells play (and can be encouraged and so cultivated to play), requires considerable research – research that is worthy of pursuit. In our view, this research will proceed more effectively if it is grounded in an organic (not a mechanistic) conception of embryonic development. Stem cell research is and should be an exercise in translational *developmental* biology.

Interpretations and metaphors matter: They can helpfully focus a researcher's attention or they can lead her astray in pursuit of fruitless research. A stem cell is not a mechanical self-contained unit – a car – being driven to work; it is an organic, dynamic, interactive cell whose potential is as much a function of its environment as its internal biology. We expect that sound science, ethics, and policy will stem from a more realistic and biological understanding of stem cells in development, and that the prospects for success are greatly enhanced within the context of systems bioethics.

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