Philosophy of stem cell biology – an introduction

Abstract
This review surveys three central issues in philosophy of stem cell biology: the nature of stem cells, stem cell experiments, and explanations of stem cell capacities. First, I argue that the fundamental question ‘what is a stem cell?’ has no single substantive answer. Instead, the core idea is explicated via an abstract model, which accounts for many features of stem cell experiments. The second part of this essay examines several of these features: uncertainty, model organisms, and manipulability. The results shed light on the form of our emerging knowledge of stem cells: mechanistic explanations. The third part of the essay sketches some key features of these explanations, which are constructed by a collaborative experimenting community.

1. Introduction
Stem cells are defined as cells that can give rise to more cells like themselves, as well as more specialized, or differentiated, cells. Though this functional definition may seem straightforward, it leaves a number of questions unanswered. Exactly what stem cells are, and the basis of their distinctive capacities, are topics of intense scientific debate. At stake in the answers are the future of regenerative medicine and our understanding of biological development. While philosophy cannot anticipate results of scientific inquiry, a number of key issues in stem cell biology can benefit from philosophical analysis. One such feature is stem cell diversity. Rather than a single clearly-defined entity, we have a bewildering variety of stem cells: human embryonic stem cells (hESC), induced pluripotent stem cells (iPSC), hematopoietic (blood-making) stem cells, mesenchymal, neural, embryonyl carcinoma cells, cancer stem cells, and many more. Is there any unity to be found in stem cell biology? And if not, how can we consider the field a science, and not merely a disparate collection of cell technologies?

Worryingly, cutting-edge molecular genetic methods only compound the problem. In the early 2000s, three different groups of researchers used high-throughput genomic methods to identify a “genetic signature for stemness” – a list of genes expressed in all and only stem cells
(Fortunel et al 2003, and references therein). Each group identified a putative signature of several hundred genes - but only one appeared on all three lists. Whether the variable results were due to different experimental techniques, heterogeneous cell populations, or nonexistence of a “stemness signature” remains unknown. Why does debate over stemness persist? Why is knowledge of stem cells so difficult to obtain? This essay proposes some answers, based on a review of recent philosophical accounts of stem cells.

Several caveats are necessary at the outset. First, much philosophical discussion of stem cells focuses on ethical controversies over use of human embryos and eggs for research. Because these ethical issues are extensively discussed elsewhere, I do not address them here. Instead, this essay examines philosophical accounts that bear on the question of stem cell diversity and knowledge. A second caveat is that this brief survey cannot fully engage with all aspects of these accounts, which hail from diverse philosophical approaches and schools of thought. I have attempted to strike a satisfactory balance of depth and breadth, indicating texts for further reading in many areas. Though the following sections defend the approach I favor, the argument is intended to display its advantages rather than definitively exclude other approaches.

The discussion focuses on three related issues, which deal, respectively, with the subject matter, methods, and results of stem cell science:

(1) nature of stem cells

(2) stem cell experiments

(3) form of knowledge in stem cell biology

Section 2 examines several different philosophical approaches to understanding the nature of stem cells: natural kinds, competing scientific theories, and abstract models. I argue that the last
of these is the most incisive, and accounts for several important features of stem cell experiments. Section 3 discusses three important aspects of these experiments: uncertainty due to evidential challenges, the role of model organisms, and manipulation of cell development by reprogramming. Insofar as these experimental strategies are successful, they yield knowledge about stem cells. Building on these results, Section 4 proposes that knowledge in stem cell biology takes the form of mechanistic explanations of cell development. Though this brief overview leaves many questions unanswered, it indicates a platform for further philosophical work on these questions, and a fresh perspective on core topics in philosophy of science and philosophy of biology.

2. What are stem cells?

The most fundamental question for stem cell research concerns the nature of stem cells themselves. Though it seems they must be cells like others that make up organismal bodies (neurons, fibroblasts, lymphocytes, *etc.*), the question of stem cell identity is more complex. This section surveys philosophical answers offered to date, arguing that an approach emphasizing scientific models best clarifies the stem cell concept used by scientists today. This concept is closely linked to both fundamental ideas about development and details of particular experiments.

2.1 Natural kinds

The most straightforward way to philosophically account for stem cells is as a special case of a more general theory. Because ‘the stem cell’ is *prima facie* a kind of cell, theories of natural kinds are a reasonable starting-point. Wilson et al (2009) defend a homeostatic property cluster
(HPC) account of natural biological kinds, which they argue applies to genes, species, and stem cells. On this Boydian account, stem cells belong to a natural biological kind in virtue of an HPC ‘held together’ by underlying causal mechanisms. The HPC view allows for variation within a kind, as well as explanatory significance of kind-membership. Properties comprising an HPC are causally basic, grounding explanations and predictions about other properties had by kind members (15-16). Wilson and colleagues offer an open-ended list of stem cell cluster properties: being morphologically undifferentiated, able to self-renew over an extended period of time, able to give rise to various differentiated cell types, developmentally derived from certain cells or tissues, located in specific parts of tissues, found in a specific microenvironment that influences behavior, and having a low rate of cell division and particular complex profile (or signature) of gene expression and presence of transcription factors (32).

There are three problems with this natural kind account. First, although they are general features of stem cells, the listed properties offer little in the way of explanatory or predictive power. So it seems incorrect to call them “basic,” as HPC must be. Instead, these properties are placeholders for characteristics currently unknown. Second, the natural kind account obscures the artificiality of some important varieties of stem cell (e.g., ESC and iPSC). These and other pluripotent stem cells (see below) are laboratory constructs with no exact natural counterparts. It is therefore misleading to classify stem cells in general as members of a natural kind. Third, the HPC account offers no guidance about stem cell diversity; the cluster properties are ambiguous. To see this, consider one crucial property of stem cells: ability to give rise to various differentiated cell types. The term “various” here covers a wide range of cell potencies – from all cell types in the body (pluripotent) to a sizable subset of these (multipotent) to only a few (oligopotent). However, self-renewing cells that give rise to one mature cell type (unipotent) are
excluded. So some well-studied varieties, including skin and germline stem cells, do not satisfy the definition. Though the HPC account is flexible enough to deflect these unipotent counterexamples, by the same token many other cells that are not considered stem cells qualify as such – including highly differentiated B lymphocytes. So the general HPC account conflicts with biological practice. Moreover, it is noncommittal about specific varieties of stem cell – is ESC, for example, also an HPC kind? Or are all stem cells members of only one kind: “the stem cell”? In the absence of details about or explanatory relations among stem cell properties, the HPC view offers no guidance on these questions.iv

2.2 Competing theories

A second philosophical approach is to treat scientific debate about the nature of stem cells as a controversy over theory-choice. Leychkis et al (2009) compare, assess, and clarify two alternative accounts of “stemness:” the state and entity theories.v The dominant entity theory asserts that stemness is a specific property had by a cell: “the property of having a certain gene or genes whose expression makes possible both the potential for self-renewal and the potential for multilineage differentiation” (ibid, 313). That is, according to the entity theory, stemness is a property of individual cells, localized to their internal genetic mechanisms, which explains their distinctive capacities for reproduction and development. The entity theory can be seen as a modified version of the natural kind account, with stemness genes in the role of clustering mechanism for HPC properties (§2.1). In contrast, the state theory asserts that stemness is a state that cells may enter or leave, not an intrinsic property of cells. The stem state is distinguished from other states of a cell by plasticity: “having many potential outcomes but no specialization” (Zipori 2004, 876). Importantly, the state theory allows stemness, and development more
generally, to be “transient and reversible,” and makes no claims about properties of individual
cells (ibid).

Leychkis et al conclude (reasonably) that current evidence is insufficient to confirm or
disconfirm either theory, and note that a future account might reconcile them. Toward this end,
they use higher-order predicate logic to clarify the state theory. Though consistent with current
data, this analysis does not clarify the challenges that must be met before theoretical debate about
stem cells can be settled, nor offer insights about stem cell diversity. So, like the natural kinds
account, Leychkis et al’s theoretical approach does not offer much guidance or clarification of
ongoing stem cell research. Elaborating the “state vs. entity” framework, Laplane (2013)
distinguishes four ontological theories of stem cells: the entity, capability, system, and state
views. The capability account is a functional counterpart of the entity theory, while the system
account emphasizes cell environments as crucial for stemness.vi These conceptual distinctions
help to clarify scientists’ positions and arguments. But treating the various accounts of stem
cells as theories in the traditional sense (i.e., sets of statements describing universal laws or
principles, amenable to logico-linguistic analysis) is somewhat misleading.

Rather than traditional analysis, Laplane (2013, ms.) uses the four-part account to shed
light on another theoretical debate in stem cell biology, over cancer stem cells. The cancer stem
cell (CSC) theory asserts that cancers, like many organs, develop from stem cells that self-renew
and give rise to other tumor cells. The extent to which CSC theory is confirmed is a subject of
intense scientific debate, with obvious clinical ramifications.vii Laplane (2013) shows that
dispute over the nature of stem cells is reprised in the CSC debate, and articulates the different
clinical implications of entity, capability, system, and state theories. She then extends this
pluralistic approach back into history, tracing the multiple strands of biological thought that
contribute to CSC theory, as well as resultant ambiguities that complicate current scientific
debate (ms.). Other historical approaches to CSC include Brandt (2012), Cooper (2009), Kraft
(2011), and Maehle (2011). These historically-informed studies situate ideas about stem cells
in broader scientific and social context, engaging experiments as well. The philosophical
approach that best complements these historical accounts focuses on models rather than theories
in the traditional sense.

2.3 Models

A third approach to the question ‘what is a stem cell?’ is to construct a general abstract model, of
which all varieties of stem cell are specific instances (Fagan 2013). The general scientific
definition provides a starting point: stem cells are undifferentiated cells that self-renew and give
rise to differentiated cells. Self-renewal is production of more cells like the parent, and
differentiation is production of cells that are more specialized than the parent. The next task is to
define these cell reproductive processes in a simple, abstract way. Both involve comparison
across cell generations. Cells reproduce by binary division; one parent cell produces two
offspring cells. Generations of cells linked by reproductive division form a lineage with the form
of a branching tree. Within a lineage, processes of self-renewal and differentiation are
complementary: self-renewal requires ‘sameness’ across cell generations; differentiation
involves change in the ‘direction’ of increased specialization.

A minimal stem model, then, would be one cell undergoing one division event, such that
one offspring cell resembles the parent, while the other is more specialized (Figure 1). But this
is too minimal. First, no two cells are similar or different in every respect. To be scientifically
useful, comparisons across cell generations must be relative to some set of variable characters C’
(e.g., size, shape, or concentration of a particular molecule). Second, most stem cell phenomena involve more than one cell division event. Assuming regular rates, the number of cell divisions $n$ serves as a time parameter, ranging from hours to decades of conventional calendar time. Self-renewal can therefore be defined as follows:

*Self-renewal* occurs in lineage $L$ if and only if parent and offspring cells have the same values for characters in $C$ for $n$ generations.

Differentiation requires an additional variable. Because differentiation is change across cell generations in the direction of specialization, the relevant comparison is not between parent and offspring cells, but between developing and mature cells. Mature cells (unlike stem cells) cluster into types that fit the HPC kinds account (§2.1). Each mature cell type is distinguished by a specialized set of character-values $M$, which includes morphological, functional, and molecular characters. Then differentiation can be defined as follows:

Cells in lineage $L$ *differentiate* over some time interval $t_1$-to-$t_2$ just in case cell character values for $M$ at $t_2$ are more similar to those of mature cells than at $t_1$.

Putting these two together, a stem cell can be defined as the unique origin (stem) of lineage $L$ for time interval $n$, characters $C$ and mature cell characters $M$. Relative to these parameters, a stem cell has maximal self-renewal and differentiation potential (Figure 2).

Several important consequences follow from this abstract model. First, it provides a unifying framework for stem cell biology, while also accounting for stem cell diversity. The model itself is unified, but requires interpretation to represent any biological target. Different combinations of values of variables $L$, $n$, $C$ and $M$ correspond to different varieties of stem cell (adult, embryonic, pluripotent, induced, neural, muscle, skin, blood, *etc.*). In this way, the model accommodates stem cell diversity. In practice, the values of variables are specified by materials
and methods of particular experiments. In this way, the minimal model accounts for stem cell biology’s emphasis on experiment rather than theory. A related consequence is that any substantive claim about stem cells is relative to an experimental context. That is, absent experimental details, claims about stem cells are massively ambiguous – we do not know what is being talked about. To gain further insight about stem cells, we need to examine experiments that aim to identify them (for ease of exposition, I refer to these as ‘stem cell experiments’).

3. Experiments

Stem cell experiments share a common basic design. First, cells are removed from an organismal source and placed them in a context in which their character-values can be measured. After the measurements are made, some of these cells are moved to a new environment, where they are allowed to differentiate. Lastly, character-values of the differentiated cells are measured. By this procedure, the model’s variables are specified (Figure 3). Results correlate character values of the organismal source, candidate stem cells, and differentiated cells.

3.1 Uncertainty

Evidential challenges begin with the fact that a stem cell experiment involves measuring cells in two different environments, while no single cell persists through both. Because cells reproduce by division, parents and offspring cannot co-exist. The second measurements are of cells descended from those measured in the first. This creates at least three evidential problems. First, self-renewal and differentiation potential cannot both be measured for a single cell. To determine a cell’s differentiation potential, that cell is placed in an environment conducive to differentiation, and its descendants measured. To determine a cell’s ability to self-renew, it is
placed in an environment that *blocks* differentiation; where its descendants are unchanged with respect to characters of interest. It is not possible to perform both experiments on a single cell. So, because stem cells are defined as having both capacities, they cannot be identified at the single-cell level.\textsuperscript{xi}

Nor does it help to separate the two capacities. Self-renewal occurs just in case parent and offspring cells are the same with respect to some characters of interest, for some time-interval of interest. A self-renewing stem cell divides to produce one or two offspring that are also stem cells: meaning that they have the same ability to self-renew as the parent (and the same differentiation potential). But that ability to self-renew is revealed, in turn, by the offspring of the offspring cell having the same capacities as the parent – and so on. The data needed to show self-renewal for a single stem cell are always one generation in the future. Thirdly, a putative stem cell’s differentiation potential is revealed by placing it in an environment conducive to differentiation, then measuring its descendants to see whether these exhibit specialized features of mature cells. But there is no generic differentiation environment; different specialized cells are elicited under different conditions. A single cell can be placed in (at most) one such environment. We cannot tell what a cell’s descendants would be like in a different range of environments, or without any experimental manipulation. For all three reasons, claims that any single cell is a stem cell are necessarily uncertain.

This uncertainty opens up space for debate about what entities qualify as stem cells, and the extent of developmental potential for any particular candidate. In addition to the debates discussed above (§2.2), there are long-running controversies over the developmental and therapeutic potential of ‘adult’ vs. ‘embryonic’ stem cells. In practice, such debates are (provisionally) settled by appealing to the “single cell standard” (Fagan 2011, 2013). A
A homogeneous population of identical stem cells would resolve the evidential problems above, because identical copies of ‘the same cell’ could be used in replicate experiments to realize the full range of self-renewal and differentiation potential for that cell. Cell homogeneity is not absolute, however, but relative to some set of characters. Moreover, because the stem cell signature is unknown, we cannot be sure that any given character-set is correct. As new characters are discovered, made accessible by new technologies, evidence for stem cell capacities must be continually reassessed and updated. Any given claim about stem cells is therefore provisional, and generalization across experimental contexts highly speculative. But within a particular experimental context, the more direct and systematic our observations of single cells and their progeny, the stronger the evidence for stem cell hypotheses. Technologies that improve our access to single cells thereby provide better evidential support for claims about stem cells. This “single cell standard” has guided stem cell biology for more than 50 years. In this sense, the field is driven by experiment rather than theories.

3.2 Model organisms

The above considerations follow from the abstract stem cell model and the basic structure of experiments that link it to biological targets. Robert (2004) takes a complementary approach to the diversity and context-specificity of stem cells, focusing on material models. In particular, Robert highlights the role of model organisms, selected from natural populations and modified to serve experimenters’ purposes, in stem cell research. Classic model organisms include inbred mice, *E. coli* bacteria, and the fruitfly *Drosophila melanogaster*. Model organisms share key traits that make them tractable and illuminating objects of study: they are small, hardy, easy to manipulate and maintain under laboratory conditions, reproduce rapidly, and exhibit phenomena
of interest in a way accessible to observation and experimental manipulation (Bolker 1995). But these very features make model organisms atypical. So generalizations from these models to other organisms must be made very cautiously.

Robert (2004) uses these ideas to account for stem cell variability and elusiveness of the stem cell signature. Each model organism, and experimental systems that use them, has its own distinctive features. Of particular concern is the use of mouse models to represent human physiology and pathology. Clinical applications in humans are a driving goal of stem cell research. Yet many experiments use animal models - primarily inbred mice (another classic model organism). To bridge the “inferential gap” between mouse models and human targets, Robert argues, stem cell biologists construct human-mouse chimeras as model organisms. These intermediate beings, of course, raise epistemic and ethical challenges of their own.

Model organisms also figure in stem cell research in another way. As noted above (§2.1), many stem cells are produced artificially by removing cells from an organismal source and placing them in artificial culture.\textsuperscript{xii} These cultured stem cells exhibit the distinguishing features of model organisms. They are selected to rapidly divide, to self-renew in artificial media, and (when placed in a suitable environment) to differentiate into all the major cell types. That is, pluripotent stem cells are designed to display stem cell capacities in a clear and accessible way. They also embody early mammalian development in drastically simplified form: a layer of undifferentiated cells in transparent artificial ‘bodies,’ which can be induced to differentiate in plain sight. So pluripotent stem cells can be considered model organisms for studying cell development. Parallel arguments can be made for tissue-specific stem cells (e.g., blood stem cells) as components of model systems for studying cell development (Fagan 2010, 2011).
The model organism concept clarifies how stem cells from different experimental contexts relate to one another. An array of model systems exhibits a matrix or network of similarities and differences. Such a network of models, or ‘field of experiments,’ is the ground of general knowledge about stem cells (§4). Several interesting consequences follow from this ‘material modeling’ view of stem cell research. Most importantly, given current debates, the different varieties of stem cell are not competing alternatives but complementary partners. The more varieties characterized, the richer the network of comparisons for the field, and the more robust any resulting generalizations. It follows that ‘oppositional’ views of stem cell research, which cast different kinds of stem cell as competing model systems (e.g., adult vs. embryonic, hESC vs. iPSC), are misconceived.

3.3 Reprogramming

Results of stem cell experiments (like many other biological experiments) are understood in causal terms. Woodward’s (2003) manipulability theory provides a satisfying account of these causal results. According to this theory, X causes Y if and only if there is a possible manipulation of some value of X, under idealized experimental conditions, such that the value of Y changes. Insofar as they resemble this idealized standard, real experiments reveal genuine causal relations among sets of entities and their properties. Stem cell experiments manipulate cell development via changes to cell environment. Of particular importance is “reprogramming,” in which cells’ developmental potential is manipulated so as to transform mature differentiated cells to pluripotent stem cells that resemble ESC. Briefly: differentiated cells are extracted from a human or mouse and cultured with a few specific genes (transcription factors). After a few weeks, about 0.5%
change to resemble embryonic stem cells, morphologically and in their developmental capacities. These are induced pluripotent stem cells (iPSC).

This experimental design suggests that a small set of genes controls cell development. But this impression is misleading; control of development is more complex. The genes that produce iPSC are transcription factors (TF). As proteins, TF specifically bind to particular regulatory sequences of DNA, which in turn affects the expression of genes nearby on the chromosome. So, altering the expression of one TF gene can make a difference to the expression of dozens, even hundreds, of other genes. TF proteins are thus “phenotypic switches” that can coordinate large-scale patterns of gene expression within a cell. The crux, however, is the binding interaction of a TF protein and a regulatory DNA sequence. Neither component has priority over the other; both DNA and protein are crucial. The causal relations revealed by reprogramming experiments are organized into complex molecular networks, not simple causal links forming a linear chain.

4. Mechanistic explanation

The above considerations indicate the form of knowledge in stem cell biology. Study of model organisms reveals the details of molecular mechanisms in specific, accessible systems. Generalizations across many experiments (notably reprogramming) describe robust patterns of cell development. These two ‘levels’ – molecular and cellular – correspond to the basic structure of mechanistic explanation, the predominant form of explanation in many fields of experimental biology (Machamer et al 2000, Craver 2007). Mechanistic explanations describe how a higher-level phenomenon works in terms of lower-level components. There is strong philosophical
consensus that these explanations describe causal mechanisms of diverse working parts, spatially, temporally, and causally organized so as to constitute the overall process or system (Fagan 2012). In the stem cell case, higher-level phenomena are stem cell capacities and their developmental outcomes; i.e., processes of cell development. These cell-level phenomena are explained by a complex system of interacting molecular parts: DNA, RNA, protein, small molecules, membranes, and so on.

The general account of mechanistic explanation clarifies the concepts of stemness and cell state, which involve both cellular and molecular levels (§2.2). In the framework of mechanistic explanation, a cell is an overall system that engages in developmental processes, functioning within an organism or tissue, interacting with other cells, etc. These cell-level activities produce effects: new cells, cell populations with different traits, more mature organisms. How all this happens is explained by organized molecular components that interact to constitute the cell state. In this way, underlying molecular mechanisms explain overall cell states and developmental relations among them. This account offers further clarification of debates over alternative views of stem cells (§2). The state account, and the idea of stemness more generally, is not a definition or theory in the traditional sense, but rather a sketch of mechanistic explanation for cell development. Scientific debates over stemness are better understood as arguments about the best way to arrive at explanations of stem cell phenomena, than as problems of theory-choice.

5. Conclusion

While the above survey does not exhaust the philosophical significance of stem cells, these three issues - nature of stem cells, experiments used to identify them, and resulting explanations –
provide a solid starting point for more extended and comprehensive philosophical accounts of
stem cell biology. Section 2 surveys philosophical accounts of the nature of stem cells, arguing
for a modeling approach rather than more traditional emphases on theories or natural kinds. The
model I propose explains a number of prominent features of stem cell biology. The variety of
stem cells is derived by different values of variables $L, n, C$ or $M$. In practice, their values are
specified by experimental materials and methods. Any substantive stem cell concept is therefore
tied to a particular experimental context. Another consequence is that it is impossible to
demonstrate by experiment that any single cell is a stem cell (Section 3). This amounts to a kind
of uncertainty principle for stem cell biology: our knowledge about them is provisional,
dependent on assumptions underwriting the ‘single cell standard’ that must be re-assessed when
the experimental context changes.

Philosophical accounts of model organisms clarify the material aspects of this epistemic
situation, while Woodward’s manipulability theory explicates the causal interpretation of results.
Reprogramming experiments, which manipulate cells’ developmental potential, are particularly
important in setting the stage for explanation of stem cell phenomena. This examination of stem
cell experiments, though brief, indicates why generalization from stem cell experiments is very
difficult, theories are less emphasized than experimental accomplishments, progress in stem cell
research is so tied to technology, and debate about ‘stem cell plasticity’ is prolonged. Finally,
building on the account of experiment, Section 4 argues that emerging knowledge of stem cells
takes the form of mechanistic explanations. This core topic in recent philosophy of biology also
offers a fresh perspective on debates over the nature of stem cells, as being about how best to
discover mechanistic explanations rather than theories in the traditional sense.
Mechanistic explanations of stem cell phenomena are constructed by combining experimental results from many different model organisms and systems. So social epistemology is also relevant for philosophy of stem cell biology (Fagan 2011). Many other core topics in philosophy of science could also be usefully re-examined in terms of stem cells: scientific realism, theories of reference, the role of values in science, laws and generalization, biological individuality, and more. All these are promising areas for future work on philosophy of stem cell biology.

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Works Cited


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FIGURE 1 Asymmetric cell division – a minimal stem cell model.
FIGURE 2 Abstract stem cell model.
FIGURE 3 Stem cell experiments – specifying model parameters.
ENDNOTES

\[\text{\textsuperscript{1}}\] See, for example, Melton and Cowan (2009, xxiv), Ramelho-Santos and Willenbring (2007, 35), the National Institutes of Health (2009), and the European Stem Cell network (2008).

\[\text{\textsuperscript{\textit{ii}}}\] That lone gene, integrin alpha-6, is not a plausible ‘master gene’ for stemness.


\[\text{\textsuperscript{\textit{iv}}}\] These considerations do not exclude the possibility of a more successful natural kind theory of stem cells. But none has yet been proposed. Laplane (2011) offers a more fine-grained classification of stem cells based on extent of potency. However, this account takes the distinction between pluri- and multipotent stem cells for granted rather than grounding it in theories of natural kinds.

\[\text{\textsuperscript{\textit{v}}}\] Robert (2004) also discusses the “state vs. entity” debate, focusing on material rather than abstract models (see §3.2).

\[\text{\textsuperscript{\textit{vi}}}\] Robert et al (2006) also defend a version of the system theory: termed the “relational” view. Laplane (ms.) uses somewhat different terminology than her (2011), distinguishing four ontological conceptions of stem cells: categorical property, disposition, system, and relation. The notion of an ontological conception may be more compatible with a modeling approach than traditional accounts of scientific theories (see §2.3).

\[\text{\textsuperscript{\textit{vii}}}\] If CSC theory is correct, much cancer therapy will need to be revised, to target cancer stem cells rather than all tumor cells.

\[\text{\textsuperscript{\textit{viii}}}\] Due to constraints of space, I can here only indicate these historical accounts, as well as those on stem cell research more generally: Cooper (2003), Dröscher (2012), Kraft (2009), Maienschein (2002, 2003), and Morange (2006).

\[\text{\textsuperscript{\textit{ix}}}\] Material in this section is covered in greater depth in Fagan (2013; see esp. Ch3, 6-7).

\[\text{\textsuperscript{\textit{x}}}\] See Fagan (forthcoming) for a more detailed version of this argument.

\[\text{\textsuperscript{\textit{xi}}}\] Single-cell transplantations that restore a particular tissue or organ in a living animal are apparently counterexamples to this claim. There are some important distinctions between these in vivo experiments and in vitro cell culture approaches to characterizing stem cells, which deserve more extensive discussion than is possible here. But, though some aspects of uncertainty are minimized by in vivo single-cell experiments, the conceptual point stands: self-renewal is inferred rather than measured and the precise extent of differentiation potential cannot be determined. Thanks to an anonymous reviewer for Philosophy Compass for raising this issue.

\[\text{\textsuperscript{\textit{xii}}}\] All known pluripotent stem cells are produced in this way.

\[\text{\textsuperscript{\textit{xiii}}}\] For history of reprogramming concepts and their significance for theories of development (especially temporal aspects and reversibility), see Brandt (2010, 2012).