Philosophy of Science

The stem cell uncertainty principle

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Abstract:	Stem cells are defined by capacities for both self-renewal and differentiation. Many different entities satisfy this working definition. Explicating the stem cell concept reveals it to be relational and relative, requiring contextualization by a cell lineage, organismal source, cell environments, and traits of interest. Not only are stem cell capacities relative to an experimental context; the stem cell concept imposes evidential constraints on the interpretation of experimental results. In consequence, claims about stem cell capacities are inherently uncertain. I discuss the implications of this result for progress in stem cell research and its public understanding.

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.[1] These two cellular processes are termed, respectively, self-renewal and differentiation. A striking feature of stem cell biology is the sheer *variety* of stem cells: adult, embryonic, pluripotent, induced, neural, muscle, skin, blood, *etc.* This diversity is exploited in political debates over stem cell funding, and complicates public discussions about stem cells and their therapeutic promise. Stem cells derived from human embryos are cast as ethically dubious alternatives to so-called "adult stem cells" or, more recently "induced pluripotent stem cells."[2] A variety of "stem cell therapies" are touted by medical professionals – some backed by solid evidence, some experimental, and some purely "snake oil."[3] The multiplicity of stem cells, complexity of techniques and terminology, and the passionate nature of debate surrounding their source and potential is such that in some quarters, "the traditional notion of stem cells as a clearly defined class of intrinsically stable biological objects that can be isolated and purified, has begun to give way… the 'stem cell' becomes a fleeting, ephemeral and mythical entity" (Brown et al 2006, 339-343).

To distinguish reasonable hopes from misleading hype, it is necessary to clarify the stem cell concept and its application in various contexts. Philosophers of science have a distinctive role to play here. Bioethicists have approached stem cells as a human reproductive technology, framing debates in terms of moral status, personhood, life and human identity. But this approach

[1] See Melton and Cowan (2009, xxiv), Ramelho-Santos and Willenbring (2007, 35), the 2011 US National Institutes of Health stem cell information page, and the 2011 "Glossary" of the European Stem Cell network. For history of the term, see Maienschein (2003), Shostak (2006).
[2] This 'oppositional' stance made possible the August 2010 injunction on federally-funded embryonic stem cell research in the US, which was imposed because competition for funds allegedly harmed adult stem cell researchers.
[3] See 'About stem cell treatment' at http://www.isscr.org/.

does not fully engage stem cell science, focusing instead on the fragment that manipulates human embryos. This paper argues that the roots of stem cell controversy are not solely in ethics, but also the core concepts and methods of stem cell researchers. I show that pluralism about stem cells, and disagreement about their potential, has conceptual and evidential grounds. This situation gives rise to a deep evidential challenge: the "stem cell uncertainty principle."[4] When clearly stated, this principle makes explicit the uncertainty inherent in the basic stem cell concept. Its constraints have important implications for progress in stem cell research, as well as public understanding of this science.

Section 2 explicates the general stem cell concept, focusing on processes of self-renewal and differentiation. This analysis reveals the key variables and parameters that must be specified for the concept to apply in actual cases; that is, to classify cells (singly or in populations) as stem cells. Section 3 summarizes the core experimental method for identifying stem cells, and shows how it dovetails with the general concept. Stem cell experiments specify the key variables and parameters for particular cases. The evidential challenge posed by these experiments is examined in Section 4. Briefly: stem cell capacities are realized only in descendants. So an individual stem cell can be identified only retrospectively; stem cell researchers literally don't know what they've got until it's gone. The problem cannot be avoided by focusing on cell populations or inventing new techniques. Section 5 considers the implications of this result, and offers suggestions for how stem cell research can progress given its evidential constraints. Section 6 summarizes the conclusions and indicates their broader significance.

Some basic tenets of cell theory are assumed throughout. Every organism begins as a single cell, which, in multicellular organisms, gives rise to all the body's cells. Cells reproduce

[4] This term is from Nadir (2006).

by binary division.[5] The life of a cell begins with a division event and ends with either a second division event yielding two offspring, or cell death yielding no offspring. Generations of cells linked by reproductive division form a lineage. Self-renewal is cell reproduction in which parent and offspring resemble one another. Differentiation, along with growth, is the core phenomenon of development: the process by which parts of a developing organism acquire diverse, specialized traits over time. These premises provide the background for further clarification of the stem cell concept.

2. Stem cell concept

Stem cells are defined as cells capable of both self-renewal and differentiation. The simplest way to conceptualize a stem cell is in terms of a cell division event that includes both processes: one cell like the parent, the other more specialized (Figure 1a). But this simple model does not capture the stem cell concept. No two cells are the same or different in *every* respect. At minimum, the cells involved in a division event (one parent and two offspring) differ in position and intercellular relations, and share some material parts, including DNA sequences. Comparisons that determine 'stemness' must be made relative to some set of characters, such as size, shape, concentration of a particular molecule, *etc*. Given a set of characters C={x, y, z…n}, values within and across cell generations can be compared, to determine relations of sameness and difference among cells in a lineage (Figure 1b).

[FIGURE 1]

[5] There are two modes of cell division: mitosis and meiosis. In mitosis, the genome replicates once before the cell divides. In meiosis, the genome replicates once, but two rounds of cell division follow, yielding four offspring cells with half the complement of DNA. Stem cell phenomena involve mitosis, so the term "cell division" here refers to that mode only.

2.1 *Stem cell capacities*

The above is still insufficient to define self-renewal and differentiation, which have temporal as well as comparative aspects. The dynamic aspect of self-renewal is conceived as the number of division cycles in which parent and offspring cells are the same with respect to some set of characters C (Figure 2a).[6] Differentiation involves change within a cell lineage over a time interval t_2-t_1. The simplest way to conceive of cellular change is in terms of a single cell with some character X (*e.g.*, shape or size), which has value x_1 at time t_1 and x_2 at a later time t_2. But not every such change counts as differentiation. A cell that changes character value from x_1 to x_2 thereby differentiates only if the change is 'directed' in at least one of two ways: toward more specialization or greater diversity. These two 'directions' correspond to two kinds of comparison: between cells of a developing lineage, and between developing and mature cells (Figure 2b). The former become more heterogeneous over time, differentiating from one another. More precisely, cells in lineage L *diversify* over time interval t_2-t_1, relative to a set of characters C, if and only if values of C vary more at t_2 than t_1. The second comparison is between cells that have completed development and those that have not. The diverse cells composing the body of a fully-developed organism are classified according to typologies that may extend to hundreds of cell types. Each of the latter is defined by a cluster of character values, C_m. A cell *specializes* over time interval t_1-t_2 just in case its character values are more similar to C_m at t_2 than at t_1.[7] The relevant set of characters is determined primarily by attributes of mature cells that are the end-points of the process.

[6] Cell cycle rate converts this to calendar time; in practice both measures are used.

[7] In many cases, however, there is not one cell fate to consider, but a whole array, each with a characteristic complex of traits (C_{m1}, C_{m2}…C_{mn}). So, in general, a cell specializes over t_1-t_2 if its

[FIGURE 2]

These considerations support the following characterizations of the reproductive processes that define stem cells:

(SR) Self-renewal occurs within cell lineage L relative to a set of characters C for duration τ, if and only if offspring cells have the same values for those characters as the parent cell(s).

(DF) Differentiation occurs within cell lineage L during interval t_1-t_2 if and only if character values of some cells in L change such that (i) cells of L at t_2 vary more with respect to characters C than at t_1, or (ii) cells of L at t_2 have traits more similar to traits C_m of mature cell type(s) than at t_1.

Putting the two together yields a general definition of 'stem cell': a stem cell is the unique stem of a branching structure organized by SR and DF, such that each branch terminates in exactly one mature cell type (Figure 2c). This minimal, abstract model[8] structurally defines a stem cell by position in a cell hierarchy organized by reproductive relations.

2.2 *Parameters*

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traits are more similar to some C_m at t_2 than at t_1. The attributes of specialized mature cells are so various that it is awkward to conceive them as values of a single set of characters. A cell can become more similar to an adult cell type either by changing values of a set of characters C (x_1 to x_2), or by changing its set of characters (C to C').

[8] 'Model' here is used in Giere's sense (1988).

This minimal model covers every case of stem cells. But on its own, it entails no predictions about cell phenomena. Representational assumptions are needed to connect its objects to biological targets. Three different representational assumptions are prevalent in stem cell biology today, interpreting the model's objects as: (i) single cells undergoing division; (ii) reproductively-related cell populations with statistical properties; or (iii) reproductively-related cell types. In addition, applying the minimal stem cell model requires specification of its key parameters and variables: temporal duration and characters of interest. Whether a given cell counts as a stem cell depends, in part, on how these parameters are specified. Table 1 summarizes the parameters associated with the major stem cell types in use today.

[TABLE 1]

In general, the shorter the duration of interest, the lower the bar to qualify as a stem cell. Most stem cell research is concerned with longer intervals, so the bar to qualify as a stem cell is higher. But there is no absolute threshold. What counts as a stem cell varies with the temporal duration of interest. Another variable is number of terminating branches in the cell lineage hierarchy. Termini of these branches are cell fates, each distinguished by a "signature" cluster of character values, C_m. The more terminating branches emanate from a cell, the greater its developmental potential. The maximum possible developmental potential is *totipotency*: the capacity to produce an entire organism (and, in mammals, extra-embryonic tissues) via cell division and differentiation. In animals, this capacity is limited to the fertilized egg and products of early cell divisions. In the late-19^{th}/early-20^{th} century, such cells were referred to as stem cells, but terminology has since shifted. The maximum developmental potential for stem cells in

the contemporary sense is *pluripotency*: ability to produce all (major) cell types of an adult organism. Somewhat more restricted stem cells are *multipotent*: able to produce some, but not all, mature cell types. Stem cells that can give rise to only a few mature cell types are *oligopotent*. The minimum differentiation potential is *unipotency*: the capacity to produce a single cell type. This classification of potencies, though imprecise, provides a convenient framework for comparing stem cells associated with different cell traits and fates (Table 1).

Finally, applying the abstract model requires criteria to judge cells the same or different with respect to a set of characters. Our only access to cells is via technologies that visualize, track, and measure them. So character values attributed to cells are very closely associated with methods of detection. Cells in adult organisms are distinguished by morphological, histological, and functional criteria, which figure prominently in typologies. Undifferentiated cells are often characterized negatively, as lacking these traits. Cell traits, fates, and technologies for distinguishing them are all closely entwined. Specifying criteria for cell character values to count as the same or different amounts to specifying a set of methods for measuring those characters. This brings us to concrete experiments that identify stem cells.

3. Methods

Methods for identifying stem cells share a basic structure of three stages (Figure 3a). The starting point is a multicellular organism, the source of cells. From this source, cells are extracted and values of some of their characters measured. These cells (or a sample thereof) are then manipulated so as realize capacities for self-renewal and differentiation. Each experiment involves two manipulations. In the first, cells are removed from their original context (a multicellular organism) and placed in a new environment in which their traits can be measured.

Second, measured cells are transferred to yet another environmental context, which allows stem cell capacities to be realized. Finally, the amount of self-renewal and differentiation is measured. Stem cell experiments[9] thus consist of two manipulations, each followed by measurement, of cells from an organismal source.

[FIGURE 3]

This basic method identifies stem cells by three sets of characters: of organismal source, of extracted cells, and of progeny cells (Figure 3b). The characters included in the first and third sets are standardized and robust across a wide range of experiments. For organismal source, these characters are species, developmental stage, and tissue or position within the organism.[10] Values of these characters are determined by choice of materials for an experiment: mouse or human; embryonic or adult; blood, muscle or a quadrant of the early embryo. Values for the other two sets of characters are measured during an experiment. For progeny cells, characters included are those of mature cell types: morphology, expression of specific genes and proteins, and function within an organism. Exactly which characters comprise the set depends on the type of differentiated cells expected. For blood cells, the relevant characters are associated with immune function; for neurons, electrochemical function; for germ cells, morphological and genetic traits of gametes. Though the set of characters varies across experiments, for any particular experiment the characters of interest are established in advance: part of the standard set

[9] Stem cell biology includes many kinds of experiment. For brevity, I refer to experiments that aim to isolate and characterize stem cells as 'stem cell experiments.' But this should not be interpreted as exhaustive of experiments in the field.
[10] Another frequently-used organismal character is genotype or strain.

of morphological, biochemical and functional traits used to classify cells in multicellular organisms.

In contrast, there are no such pre-established criteria for inclusion in the set of characters of extracted cells – *i.e.*, presumptive stem cells. These characters vary widely across experiments, shifting rapidly in response to technical innovations and new results within the field. Yet measurement of their values is the linchpin of stem cell experiments. Experiments aimed at isolating and characterizing stem cells succeed just in case they reveal the "signature" traits of stem cells from a given source. Relations among values of these variables map features of organismal source and differentiated descendants onto a 'stem cell signature,' entailing many predictions. A predictive model of this sort would describe robust relations between the values of variable characters in these three domains. We do not yet have such a model, however; 'mapping' relations among source, signature, and progeny are largely unknown, even for the best-understood stem cells. Indeed, the 'stem cell signatures' we have are at best provisional. An important goal of stem cell research is to flesh out this speculative sketch. But here the stem cell concept itself poses a serious challenge.

4. Uncertainty

Stem cell experiments involve two sets of measurements, both of which provide data about characters of single cells. *But no single cell persists through both sets of measurements*. Cells reproduce by division, so descendents and ancestors cannot co-exist. The second set of measurements is of cells descended from those measured in the first. Self-renewal and differentiation potential are measured after realization of these capacities in controlled environments: the second set of measurements. A single stem cell, therefore, can be identified

only retrospectively. At the single-cell level, stem cell researchers literally don't know what they've got until it's gone.

There are three distinct evidential problems here. 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 self-renewal ability, the cell is placed in an environment that is conducive to cell division *without* differentiation, and its descendants measured. It is not possible to perform both experiments on a single cell. Since stem cells are defined as having both capacities, stem cells cannot be identified at the single-cell level. Second, the capacity for self-renewal cannot be decisively established for any stem cell. An offspring cell with the same capacities as a stem cell parent has the same potential for differentiation and for self-renewal. Even if both could be measured for a single cell (which they cannot), it is the offspring of the offspring cell that indicates the latter's capacities. The relevant data are always one generation in the future. Experimental proof that a single cell is capable of self-renewal is infinitely-deferred. Third, in any experiment, differentiation potential is realized in a range of (highly artificial) environments. But these data cannot tell us what a cell's descendants would be like in a different range of environments – in particular, physiological contexts. There is, inevitably, an evidential gap between a cell's capacities, unmanipulated by experiment, and their realization in specific, highly artificial, contexts. For all three reasons, claims that any single cell is a stem cell are inevitably uncertain. This uncertainty admits diverse, even arbitrary, operational criteria for self-renewal, and underpins perennial debate over the extent of differentiation potential in stem cells from adult organisms.

These evidential limitations of stem cell experiments have been likened to the Heisenberg uncertainty principle, which states that a particle's mass and velocity cannot be simultaneously measured. In physics, the procedure used to determine the value of one alters the value of the other. The analogy suggests that measurement itself is the problem; *e.g.*, "…we cannot determine both the function of a cell and its functional potential…[because] our determination of a cell's function at a given point in time interferes with an accurate determination of its developmental potential" (Nadir 2006, 489), and we cannot rule out the possibility that "the investigator might be forcing the stem-cell phenotype on the population being studied" (Zipori 2004, 876). But for stem cell biology, the problem is not measurement of cells *per se*, but their transfer to different environmental contexts. Stem cell capacities are realized and measured in cells descended from 'candidate' stem cells, in different environments (for differentiation potential). Potten and Loeffler (1990) articulate the issues incisively:

> The main attributes of stem cells relate to their potential in the future. These can only effectively be studied by placing the cell, or cells, in a situation where they have the opportunity to express their potential. Here we find ourselves in a circular situation; in order to answer the question whether a cell is a stem cell we have to alter its circumstances and in so doing inevitably lose the original cell and in addition we may see only a limited spectrum of responses… Therefore it might be an impossible task to determine the status of a single stem cell without changing it. Instead one would have to be satisfied with making probability statements based on measurements of populations (1009).

It might seem that stem cell biologists can avoid these problems by shifting their focus to cell populations. Representational assumptions (ii-iii) allow for exactly this (see §2 above). Two kinds of model, stochastic and compartmental, yield hypotheses about stem cell

populations.[11] But experimental support for these hypotheses depends on hypotheses about single stem cell traits. Here I address stochastic population models only; an analogous argument can be made for compartment models.[12] Stochastic population models of stem cells are based on the following assumptions. Any population of cells experiences some number *n* divisions over a period of time τ, such that the population grows, diminishes, or remains constant in size. Any dividing cell in the population has a certain probability of undergoing each of three kinds of division: both offspring like the parent (*p*), one offspring like the parent (*r*) or no offspring like the parent (*q*), where $p + r + q = 1$. Relations among *p*, *r*, and *q* values entail general predictions about cell population size (growth, decrease, or "steady-state"), and equations that predict mean and standard deviation in population size, probability of stem cell extinction, and features of steady-state populations are derived.[13] In these equations, *p* is the fundamental parameter. Testable predictions require that its value be estimated. This is done by estimating the coefficient of variation for stem cell number in populations of the same age produced by division from a single founding stem cell. The data required for such an estimate are numbers of stem cells in replicate colonies, each originating from a single stem cell.

Given such an estimate, a stochastic stem cell model predicts features of cell population kinetics, which can then be compared with experimental data. But the hypothesis thereby tested is *not* that 'founder' cells are stem cells. Rather, it is that stem cell population size is regulated so as to yield predictable population-level results from randomly-distributed single-cell capacities. Testing this hypothesis requires identifying stem cell populations. Stochastic models make predictions, *given* the assumption that 'founding elements' are stem cells. All these

[11] Terms from Loeffler and Potten (1997).
[12] [reference removed for blind review]
[13] Details in Vogel et al (1969).

predictions hinge on estimation of the fundamental parameter *p*, the probability that a stem cell undergoes self-renewal. This parameter is estimated from the pattern of variation in a set of replicate colonies, initiated by a single "stem element." But in order for experiments to be *replicates*, all the stem elements for the set of colonies must be assigned the same probability values for *p* and (1-*p*); *i.e.*, the same capacities for self-renewal and differentiation. So experimental test of a stochastic stem cell model depends on the assumption that the cell population measured is homogeneous with respect to these characters. This is exactly the evidence that the stem cell uncertainty principle ensures we cannot get. Stochastic population-level stem cell models therefore do not avoid the evidential challenge above.

To sum up: stem cell experiments, no matter how technically advanced at tracking and measuring single cells, cannot resolve stem cell capacities at the single-cell level. This is because we cannot directly measure a single cell's capacity for self-renewal or differentiation, separately or together. To measure both self-renewal and differentiation potential for a single cell, and to elicit the full range of a cell's potential, multiple 'copies' of that cell are needed - a homogeneous cell population of *candidate* stem cells. Thoroughgoing focus on cell populations cannot get around this problem, since evidence for population-level models of stem cells also depends on the assumption of a homogeneous 'founder' stem cell population. The 'uncertainty principle' is an unavoidable evidential constraint for stem cell biology.

5. Progress

How, then, should stem cell biologists proceed? In practice, the dominant strategy is to adopt a 'single-cell standard;' that is, to assess progress not in terms of hypotheses, but experimental methods. Better experimental methods improve our access to single cells. Current "gold

standards" for stem cell experiments are articulated in exactly these terms. These standards are implemented somewhat differently for stem cells with different potencies. For 'tissue-specific' stem cells, the gold standard is a single-cell transplant leading to long-term reconstitution of an animal's tissue or organ. An ideal pluripotent stem cell line behaves as a single cell, exhibiting the same traits in the same culture environment, so self-renewal or differentiation capacities can be realized on demand.[14] But across the entire field, technologies that enhance our ability to isolate or track single cells are quickly adopted and reported as advances.[15] Post-genomic and micro-imaging technologies are increasingly important in stem cell biology, for this reason. But the single-cell standard dates back to post-WWII experiments with cultured cells and transplantable tumors in inbred mice. The first method for measuring stem cells was announced as "a direct method of assay for [mouse bone marrow] cells with a single-cell technique" (Till and McCulloch 1961, 213).

This approach is evidentially well-founded. The single-cell standard, applied across many stem cell types (i.e., experimental contexts), supports the assumption of homogeneity on which all stem cell models depend. An experiment that meets the standard begins with a single cell in a controlled environment, with all relevant signals that could impact the cell taken into account. If all other cell reproduction in this environment is blocked, or products of the founding cell can be distinguished from all other cells, then results reflect the reproductive output of a single starting cell, and no others. Measured stem cell capacities are then unambiguously attributed to that cell *in that environment*. Technologies that track a single cell's reproductive output over time, combined with techniques that measure character values of single cells, can

[14] "Gold standards" from *Fundamentals of Stem Cell Biology* (Cowan and Melton 2009) and the International Stem Cell Initiative's characterization of hESC lines (Adewumi et al 2007).
[15] For recent examples, see special issues of *Nature Reviews Genetics* (April 2011) and *Nature Cell Biology* (May 2011).

yield data of this sort. In this way, technical innovations guided by the single-cell standard can bolster evidence for stem cell models – but only relative to the environment in which stem cell capacities are realized. More general results are obtained from replicate experiments using a range of environments. If the same environment tends to elicit self-renewal of the same duration and/or differentiation into the same cell types, while different environments reliably yield different results, this indicates that the cell population from which replicates are drawn is homogeneous with respect to stem cell capacities. Of course, populations homogeneous with respect to *one* set of character values need not be homogeneous with respect to others. But sorting cells into populations homogeneous for many measurable traits is the best we can do, since stem cells cannot be identified in advance.

So the 'stem cell uncertainty principle' does not block progress in stem cell research. But, since the possibility of heterogeneity in stem cell capacities cannot be completely ruled out, hypotheses about stem cells can never be fully and decisively established. Stem cell experiments can provide good evidence for hypotheses at the single-cell level, but only relative to the set of characters used to specify a homogeneous sub-population. As new cell traits are discovered and made accessible to measurement, the assumption of homogeneity must be continually reassessed and revised. All substantive models of stem cells are therefore necessarily provisional, and become obsolete when new characters and environments are introduced. This evidential constraint necessitates a mode of collaboration in stem cell research that gives the lie to the idea that the field is essentially a competition of models and methods in a 'race to the cure.' Improved single-cell methods applied to all available stem cell types gives rise to a whole constellation, or network, of improved models. In this way, guided by experiment, the entire field moves forward together.

6. Conclusions

The basic stem cell concept is relational and relative. So stem cells are not defined absolutely, but relative to an organismal source, cell lineage, environments, traits and a temporal duration of interest. Experimental methods for identifying stem cells specify these parameters. In any actual case, therefore, stem cells must be understood in terms of experimental methods used to identify them. The stem cell uncertainty principle imposes evidential constraints on these methods, however. Several consequences follow. First, all stem cell claims are provisional, dependent on an assumption of cell homogeneity that must be continually reassessed as research moves forward. Second, stem cell pluralism is not a symptom of incomplete understanding, but follows from the general stem cell concept. Claims about stem cells based on different elaborations of the basic model do not conflict. The diversity of stem cells should not be a source of contention, but a positive resource for inquiry. Finally, technical innovations that increase experimenters' ability to measure and track single cells can bring about a situation in which experiments can provide strong evidence for hypotheses about stem cells. 'Single-cell' technologies are thus an important form of progress in stem cell biology, with evidential significance.

Acknowledgements

[removed for blind review]

References

Adewumi, O., *et al*. (2007), "Characterization of human embryonic stem cell lines by the International Stem Cell Initiative", *Nature Biotechnology* 25: 803-816.

Brown, N., Kraft, A., and Martin, P. (2006), "The promissory pasts of blood stem cells", *BioSocieties* 1: 329-348.

Giere, R. (1988), *Explaining Science*. Chicago: Chicago University Press.

Loeffler, M., and Potten, C. S. (1997), "Stem cells and cellular pedigrees", in: Potten, C. S. (ed.) *Stem Cells*. London: Academic Press, 1-27.

Maienschein, J. (2003), *Whose view of life?* Cambridge, MA: Harvard University Press.

Melton, D.A., and Cowan, C. (2009) "Stemness: definitions, criteria, and standards", in: Lanza, et al (eds.) *Essentials of Stem Biology*, 2nd edition. San Diego, CA: Academic Press, pp. xxii-xxix.

Nadir, A. (2006), "From the atom to the cell", *Stem Cells and Development* 15: 488-491.

Potten, C. S., and Loeffler, M. (1990), "Stem cells: attributes, cycles, spirals, pitfalls and uncertainties", *Development* 110: 1001-1020.

Ramalho-Santos, M., and Willenbring, H. (2007), "On the origin of the term 'stem cell'", *Cell Stem Cell* 1: 35-38.

Shostak, S. (2006), "(Re)defining stem cells", *BioEssays* 28: 301-308.

Till, J.E. and McCulloch, E.A. (1961), "A direct measurement of the radiation sensitivity of normal mouse bone marrow cells", *Radiation Research* 14: 213-222.

Vogel, H. *et al.* (1969), "Stochastic development of stem cells", *Journal of Theoretical Biology* 22: 249-270.

Zipori, D. (2004), "The nature of stem cells", *Nature Reviews Genetics* 5: 873-878.

Figure
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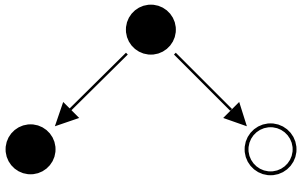
Figure 1 Simple stem cell model: (a) single cell, (b) cell population.

A.



B.

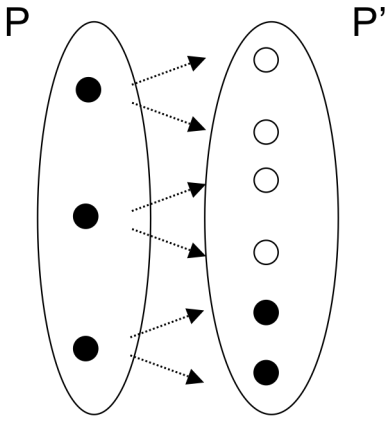
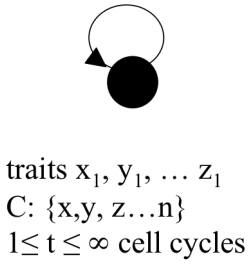


Figure 2 The stem cell concept: (a) self-renewal, (b) differentiation, (c) both. Arrows represent cell reproductive processes, variables represent key parameters (see text).

A.



B.

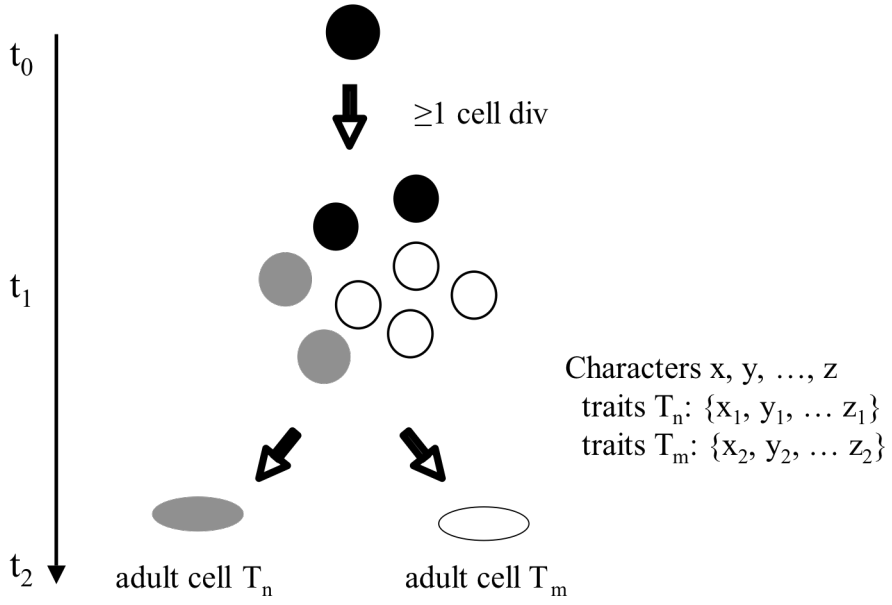


Figure 2, cont.

C.

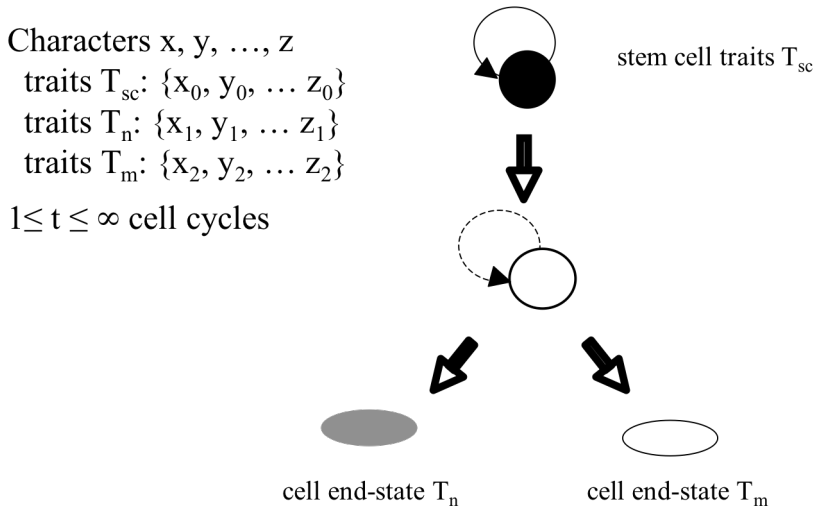
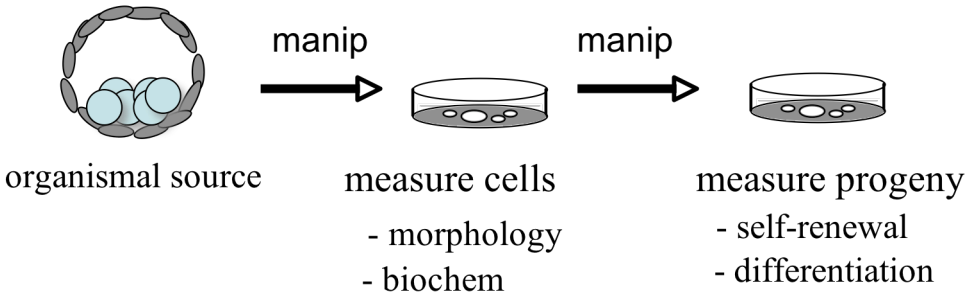


Table 1 Stem cells, classified in terms of the general model and its key parameters. (For simplicity, time intervals are left approximate and only characters are indicated, not specific values. The latter are diverse; 'various' indicates that no standard is widely-accepted for a stem cell type.)

Stem cell	Characters	Time interval/ duration	Potency	Source
ESC	shape, size, cell surface markers, gene expression	indefinite (>50 cycles)	pluripotent	early embryo inner cell mass
HSC	various	various (wks-decades)	multipotent	bone marrow, cord blood, peripheral blood
NSC	morphology, cell surface markers, nerve function	months-years	oligopotent	brain (adult and embryonic)
iPSC	shape, size, cell surface markers, gene expression	months-years	pluripotent	differentiated cells (various tissues)
epiSC	shape, size, cell surface markers, gene expression	months-years	pluripotent	early embryo inner cell mass
GSC	shape, size, cell surface markers, gene expression	months-years	pluripotent	genital ridge (embryo)
CSC	various	?	?	cancer (leukemia)
EC	shape, size, cell surface markers	weeks-months	pluripotent	cancer (teratocarcinoma)
epiderm	morphology, cell surface markers	years	unipotent	skin
hair	morphology, cell surface markers	years	unipotent	follicle

Figure 3 Basic design of stem cell experiments: (a) experimental procedure, (b) results.

A.



B.