Philosophy of stem cell biology: an integrated approach

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Stem cells are self-renewing sources for organismal development at the cellular level. They are defined by two capacities pertaining to cell division: self-renewal, which yields more cells of the same type; and differentiation potential, which yields more differentiated cell types. The hope that motivates stem cell research is that these capacities can be controlled for therapeutic use, to regenerate and repair human tissues and organs. Today, the dominant strategy for realizing these hopes is to characterize developmental effects at the single-cell level. This strategy hinges on acquiring and integrating knowledge from diverse experimental settings. By examining and critiquing these experimental methods, philosophers of science could play a role in helping realize, or clarifying the limits of, the hopes of stem cell research. An integrated historical and philosophical approach can, I argue, best satisfy this role.

Currently, there are two distinct "gold standards" for experimental success in stem cell biology. These correspond to the two main branches of stem cell research, focused on adult and embryonic stem cells, respectively. The gold standard for embryonic stem cell research is creation of a cell line with unlimited cell division (self-renewal) and potential to differentiate into all cell types of the adult organism (pluripotency) under controlled culture conditions. The gold standard for adult stem cell research is to prospectively purify cells with surface markers, transplant one cell directly into a host, and observe long-term self-renewal and reconstitution of the relevant tissue or organ. The two standards are obviously different; one a material object exemplifying features of early development, the other an experimental method employing animal bodies. Yet the aim of stem cell research is to fit these heterogeneous standards together to yield a single therapeutic strategy: produce stem cells with the desired features under controlled conditions, and transplant them to living organisms to regenerate diseased or damaged tissues and organs. This is obviously a task for scientists and clinicians, not philosophers and historians. Yet the latter, together, can provide a critical perspective on stem cell research which may assist the former.

Both these gold standards can be traced to exemplars (models) established at key moments in the history of stem cell research. The exemplars for embryonic stem cell research are the human embryonic stem cell lines cultured by James Thomson and colleagues in 1998. This technical breakthrough also set up the therapeutic goal of stem cell research, transforming a tool for genetic manipulation of mice into the centerpiece of a new biomedical field with deep implications for our theories of biological development. The exemplar for adult stem cell research is the strategy used to isolate and characterize blood stem cells, pioneered in 1988 by Irv Weissman and colleagues. This earlier turning point linked therapeutic success of bone marrow transplantation to models of blood cell development. Blood stem cells continue to serve as the model for epistemic and therapeutic success in stem cell research, being the first non-cancerous mammalian stem cells to be isolated, the first characterized at the molecular level, and the first used in routine clinical practice.

The history of blood stem cell research reveals several changes associated with establishment of the HSC standard. These include: an increase in collaborative research, a shift from biophysical to developmental models of stem cells, and increased emphasis on studying single cells instead of heterogeneous cell populations. These changes are reflected in the models used to explain experimental results, which take the form of cell lineage hierarchies tracing developmental pathways that stem from a single originating

cell. After 1988, the organization, model and method of the HSC community were quickly extended to other experimental systems: from mouse to human, from blood to other organs and tissues, from normal cells to cancers. For each new system, HSC served as exemplar and basis for comparison. The resulting network of experimental systems comprises the epistemic community of adult stem cell research today. Our current knowledge of adult stem cells is distributed across this patchy network of cell lineage models grounded in diverse experimental systems. Relations of similarity and difference to blood stem cells are an organizing motif in this network. The cancer stem cell model, a general theory of tumor growth and metastasis, is a new addition to this network, itself an exemplar coordinating diverse experimental systems. Knowledge of adult and cancer stem cells emerges from interconnections and comparisons among these diverse systems, rather than from crucial experiments testing general theories or laws.

Origins of the current standard for embryonic stem cell research also reveal comparative relations among diverse experimental systems. But in this branch of stem cell biology, the role of exemplar passes from one experimental system to the next: from cultures of spontaneous testicular tumors in mice in the 1950s, to cultures derived from mouse embryos in the 1980s, to human embryonic stem cell lines in the late 1990s. Induced pluripotent stem cell lines, recently derived from adult cells dosed with specific transcription factors, are shaping up to be the newest exemplars in this sequence. However, earlier exemplars, as well as related models, remain on the scene. As in the adult branch of stem cell research, knowledge of stem cells emerges out of interconnections among diverse model systems. As the role of exemplar is passed from one system to another, an overall trend emerges, of increasingly efficient display of the defining stem cell capacities (self-renewal and pluripotency) in a simple model of early human development.

In both branches of stem cell biology, the history of relations among these experimental systems is vital to understanding the current epistemic landscape. Looking forward, the therapeutic goal of stem cell research provides an additional evaluative dimension. The aim of stem cell research is a cell (or cell population) that can be introduced into a human body to safely regenerate a specific tissue or organ. Achieving this aim requires models that can successfully predict what cells will do when let loose in the body. So the driving task for stem cell research is to bring the two branches together, minimizing gaps and conflicts between their distinct, historically-contingent networks of comparison. This is the epistemic tension driving the current push toward standardization and translational research. Integrated history and philosophy of stem cell research offers a perspective for examining and critiquing these ongoing developments in stem cell research.