Book Review[1]

The Philosophy of Stem Cells

Melinda Bonnie Fagan: Philosophy of Stem Cell Biology: Knowledge in Flesh and Blood. Palgrave Macmillan, 2013, xx +274pp, £66.00 HB

Melinda Fagan's book on the philosophy of stem cell biology is a superb discussion of this exciting field of contemporary science, and the first book-length philosophical treatment of the subject. It contains a detailed and insightful examination of stem cell science, its structure, methods, and challenges.

The book does not require any previous knowledge of stem cell biology —all the relevant scientific details and concepts, the central experimental procedures and results, as well as the historical development of the field, are presented in as clear and accessible a way as possible. The presentation of the science starts in Chapter 1, with a general characterisation of stem cell biology, and continues throughout the book, with every chapter deepening and complicating the initial picture. Fagan's lucid style makes even the more technical and detailed discussions of the research on human embryonic stem cells (Chapter 7) and on blood stem cells (Chapter 8) easy to follow.

After the first introductory chapter, the book is comprised of three parts. In Part 1 (Chapters 2–4), the focus is on fundamental conceptual issues in stem cell biology. Part 2 (Chapters 5–8) takes stem cell biology as a case study to examine more general debates in philosophy of biology, such as mechanistic explanation, the role of genes, model organisms, the epistemology of experiment, and the role of values in science. Finally, Part 3 (Chapters 9 and 10) concerns the connections between stem cell biology, on the one hand, and systems biology and clinical medicine, on the other. There is no room here to discuss in any detail the many interesting arguments and insights of the book. Rather, in what follows I will present the general methodology of the author, as well as some key arguments of the book.

A central feature of stem cell biology that it shares with other experimentally oriented sciences, is, as Fagan stresses, its lack of general theories like the ones we find in physics. On the contrary, it is structured around models and experiments. Indeed, it is characterised by a bewildering variety of models and experiments, which at first sight make stem cell science seem disunified. This apparently puzzling situation represents an important methodological challenge for the philosopher of science: how is such a science to be approached? More generally, how is an experimental science to be analysed philosophically? Fagan's answer to this challenge is to adopt scientists' practice of modelling. This modelling approach is

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central to Fagan's methodology. Thus, in Chapter 2 of the book, she constructs what she calls an 'abstract stem cell model' that is based on the two fundamental processes connected to stem cells, self-renewal and differentiation, and that functions as a 'minimal unifying framework' (45) for stem cell research. The construction of this model constitutes the starting point of Fagan's analysis and the point of departure for a detailed examination of stem cell experiments.

The abstract stem cell model shows that, despite the absence of a general theory, stem cell biology is not a disunified science. Rather, there exist a core stem cell concept, exhibited by the abstract model, with the various stem cell concepts we find in the literature being instances of that. Representational assumptions and parameters left undetermined by the model are specified by experimental methods used to identify stem cells and link the abstract model to stem cell experiments.

These parameters show the relative character of the stem cell model. Take for example, the parameter of temporal duration: depending on how one specifies it, a given cell may or may not count as a stem cell. Crucially, Fagan uses the abstract model to identify a 'deep conceptual divide' in stem cell methods, which gives rise to the two branches of stem cell research: pluripotent and tissue-specific research, the former focusing on pluripotent stem cells and the latter on stem cells restricted to a particular tissue.

Ultimately, however, what unifies stem cell biology as a science is not a shared model or experimental method, but the therapeutic goal that underpins the ethical values internal to stem cell research, as argued by Fagan in the last chapter of the book. In contrast to the traditional value-free view of science, Fagan takes this clinical goal to be constitutive of stem cell biology.

In general, the discussion of Chapter 2 reveals Fagan's viewpoint on stem cell biology, which she characterises by three basic themes that run throughout the book and concern how knowledge in stem cell research emerges from the interaction and unification of various kinds of components, such as abstract and concrete models, experiments, and concepts from diverse fields. These themes are *interaction*, *pluralism*, and *unification*.

Chapters 3 and 4 look more closely on problems associated with the structure of stem cell experiments. In Chapter 3, Fagan discusses two inferential challenges in stem cell biology: whether experimental data on cell populations can support hypotheses about single cells, and the problem that arises from the impossibility to measure directly stem cell capacities of a single stem cell ('the stem cell uncertainty principle'). Fagan's solution to the second problem involves recognising the relativity of inferences about stem cells' capacities to the particular environmental context and their provisional nature.

To overcome these problems, a conceptual revision has been proposed by some stem cell researchers, the 'stemness alternative' (Chapter 4). According to the advocates of that account, the defining characteristic of stem cells is 'accessibility of many differentiation states' (71), rather than a universal stem cell signature. Since such a signature is presupposed by stem cell research, this view is a serious challenge. Although Fagan agrees with some claims made by proponents of the stemness account (e.g. that stem cell signatures are always relative to an experimental

context), her assessment of this view is largely negative.

Chapters 7 and 8 focus on the pluripotent and tissue-specific branches of stem cell research, respectively. In Chapter 7, Fagan offers a detailed picture of how stem cell research is organised, by examining the construction of what she calls the 'pluripotency network'. The development of this network of pluripotent stem cell lines spans more than five decades, from the 1960s, when the first cell line was constructed, to the present. Fagan convincingly argues that stem cell lines have to be viewed as model organisms —simple models to study development. Various relations of similarity and contrast exist among different stem cell lines. Generalisations about stem cell phenomena result from comparisons across various model organisms, rather than by simple inferences from model to non-model organisms. Interestingly, this leads to an argument for the importance of embryonic stem cell research, often regarded as controversial: since human embryonic stem cells are at the centre of the pluripotency network, removing them would 'disrupt the epistemic organisation of pluripotency research as a whole' (169).

In Chapter 8, Fagan describes how experiments in stem cell biology involve a community of research teams, rather than a single laboratory. Thereby, she presents a community-level account of experiment, by focusing on the main model system of tissue-specific research, blood stem cells. Social experiments result in abstract models that are 'community achievements' (194) and are closely connected to experimental methods.

Explanations of stem cell phenomena are mechanistic explanations. In Chapter 5, Fagan examines such explanations by asking: in virtue of what does a mechanistic description explain? After dismissing an answer that is based on laws, as well as one that is based on causal relations, she proposes a new account of mechanistic explanation grounded on the concept of jointness.

Mechanistic explanations, according to Fagan, are constitutive explanations: they explain how a given mechanism produces a particular behaviour in terms of the behaviour of the components that constitute the mechanism. Jointness refers to the 'working together of parts' (91) of a mechanism and is at the heart of mechanistic explanation. An example of jointness is the 'lock and key' model of enzyme action: an enzyme binds to its substrate to form an enzyme-substrate complex. Here, neither the enzyme nor the substrate alone can play the causal role that the enzyme-substrate complex plays in catalysing a reaction. Rather, the effect is produced by the two components acting jointly.

Although the jointness account of mechanistic explanation looks promising, it is not entirely clear how it differs from an account of mechanistic explanation based on causal relations. Fagan says that, to form a complex, the properties of the components have to 'mesh' with each other. But isn't the notion of 'meshing' a causal notion? Moreover, for Fagan, a mechanism is itself a complex of interacting components and its activity is the joint activity of its components. However, do all mechanisms involve such complexes? If they do, then one has to explain how we can distinguish between different mechanisms, since the most inclusive complex in this case would be the whole organism. If, on the other hand, they do not, then there exist other sorts of interactions in experimental biology that mechanistic explanations have to take

into account.

The joint account of mechanistic explanation is incompatible with attributing a privileged explanatory role to genes. This argument is presented in Chapter 6, where it is convincingly shown that cell reprogramming experiments reveal complex molecular mechanisms, and not genes, to be the actual specific difference makers in stem cell experiments. Here, Fagan examines Waddington's famous landscape model, first proposed to represent the relation between genetics and embryology. Waddington's model has been deployed by stem cell biologists as a helpful device to represent reprogramming experiments, where points on the landscape represent cell states. In Chapter 9, Fagan again uses the landscape model in order to visualise the interdependency of stem cell and systems biology, where the underside of the landscape corresponds to the modelling approach of systems biology, while the top-side corresponds to stem cell experiments. Fagan argues that the contribution of systems biology to mechanistic explanations of cell development is crucial, but the role of concrete experiments is indispensable. In this chapter and the last, the author suggests possible future directions for stem cell research.

To conclude, this book, which fills a major gap in contemporary philosophy of science, will be of interest to all philosophers of biology, to philosophers interested in experimental sciences and scientific practice, as well as to stem cell researchers themselves. As an extended discussion of the philosophy of stem cell biology, it will constitute a central work for years to come. The book serves as an ideal point of departure for conducting further philosophical research on the fascinating field of stem cell science, as well as an exemplar for how to approach philosophically today's experimental sciences; a truly impressive achievement.

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