Collaboration, toward an integrative philosophy of scientific practice[1]

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Introduction and overview

A shared theme of this session is collaboration as remedy for polarized debate. My account of collaboration has three interrelated aims: to bring practices of stem cell biology into the sphere of philosophy of science; to expand the philosophical framework for studying experimental fields so as to encompass their social dimensions; and to bridge a longstanding gap between philosophical and sociological accounts of science. I shall discuss each briefly, noting the points of interrelation that anchor the argument to follow.

Stem cell biology, like biomedicine more generally, has received little attention from philosophers of science. Those philosophical studies that do engage the field emphasize its historical, ethical and political dimensions.[2] Epistemic dimensions of stem cell research – its foundational concepts, theoretical commitments, evidential standards, and advancement of knowledge – are discussed (if at all) in relation to its social and political aspects. In stem cell biology, it would seem, the social and the epistemic are inextricably combined, assuming that philosophical engagements with the field track its conceptual lineaments.

[1] What follows is a slightly augmented version of my presentation at SPSP2. If the organizers think it suitable, a longer and more polished version of the argument will be provided for the special journal issue.
[2] The bioethical literature on stem cells is immense. Recent studies within the ambit of history and philosophy of science include: Hauskeller 2004, Hauskeller 2005, Moreira and Palladino 2005, Maienschein 2009, and essays in special issues of *Science as Culture* (March 2008 and December 2008) by Kim, Martin et al, Stephens et al, and Testa.

This assumption is, I think, warranted. Yet the epistemic dimensions of stem cell research deserve greater attention than they have heretofore been given. Knowledge-production in this field involves levels of social organization beyond that of individual researchers or small research teams. Its epistemic practices are not adequately represented in terms of individuals' observations and hypotheses, nor of justificatory arguments that appear in research reports. So the traditional tools of philosophy of science are not well-suited to the study of stem cell biology. The point generalizes to other interdisciplinary experimental fields with complex subject matter – many areas of contemporary biomedicine, human and social sciences, and engineering. New tools are needed, to study the social epistemology of these sciences. Here, I take the epistemic practices of stem cell biology to be representative.

The counterpart of a physical theory, in experimental biomedicine, is a model of potential clinical significance. Such models are constructed not by individual researchers or a single research team, but by experimental communities involving multiple laboratories and dozens of researchers. In stem cell biology, knowledge takes the form of models of cell development (Figure 1). Such models are constructed, tested and adapted to clinical aims by large experimental communities comprised by interacting working groups, laboratories, sub-fields, fields, and disciplines. For example, a single node of the model shown in Figure 1 (HPC, second from top) was established through the combined effort of more than 40 researchers from nine laboratories, five nations and three disciplines. The locus of knowledge-production in stem cell biology, and biomedicine more generally, is the *experimenting community*. Philosophical engagement with experimental sciences of such complexity demands a framework that deals straightforwardly with their collaborative social epistemology. And if our understanding is to issue in applications – that is, significant clarification and useful critique – then this

philosophical framework must itself effect a collaboration with empirical science studies - socio-historical accounts of ongoing scientific practice.

[FIGURE 1]

There is, however, a significant obstacle to such a collaborative framework: the longstanding tension between sociological and philosophical approaches to science. This tension manifests in a number of dichotomies, which ground studies of science in oppositional terms: theory *vs*. experiment, pure *vs*. applied, epistemic *vs*. social. In such a dichotomous setting, social epistemology of scientific practice is fragmented and stymied from the outset. So a new framework is needed, to overcome these entrenched dichotomies.

For my purposes, the most problematic of these concerns the relation between epistemic standards, the basis for critically evaluating scientific knowledge and methods, and standards used in scientific practice, the value-laden results of negotiated agreement. Decades of controversy over social construction of scientific knowledge have bequeathed us a dichotomous understanding of this relation: either epistemic standards and standards in practice coincide, or they are decoupled. In the former case, epistemic standards are socially constructed in scientific practice, and their critical bite vitiated insofar as these construction processes are understood. In the latter case, epistemic standards are independent of our scientific practices, and arguably irrelevant to them.[3]

I propose to replace this unsatisfactory dichotomy with an integrated account of epistemic standards in scientific practice, thus effecting a collaboration between critical philosophy and

[3] I examine this dichotomy in detail in Fagan (under review).

empirical science studies. I do so by examining the concept of collaboration: first in general, then in the context of stem cell research.

Collaboration: a general account

To understand collaboration in general, I look to analyses of collaborative activity by philosophers of social action. Their work provides a perspective on collaboration that is philosophically rigorous, intended for general application, and unrelated to the entrenched oppositions concerning social epistemology of science. These analyses focus on the distinctive attitude of joint intention (also referred to as collective or shared intention). Analyses of this attitude vary considerably. For example, on Michael Bratman's reductive account (1999), shared intention is identified with interlocking individual intentions, while Margaret Gilbert analyzes the concept in terms of an irreducibly plural subject (1989, 2006).[4] However, abstracting these differences yields a thin consensus account of the attitude distinctive of social action. The consensus view is that collaborative activity involves:

(1) a shared goal,

(2) participant means taken to it,

(3) coordination of diverse means among participants, and

(4) a public context for all of the above.

[4] On Bratman's analysis (1999), we intend to J if and only if:
(1) (a) I intend that we J, and (b) you intend that we J.
(2a) (1a) in accordance with and because of (1a), (1b) & meshing subplans.
(2b) (1b) in accordance with and because of (1a), (1b) & meshing subplans.
(3) (1a), (1b), (2a) & (2b) are in a public context.
On Gilbert's analysis, (1989) two or more individuals have a collective intention to A if and only if they constitute the plural subject of an intention to A; alternatively, persons X and Y collectively intend to do A if and only if they are jointly committed to intend as a body to do A (2006).

Some clarifications are needed here. A 'shared goal' is not merely had by multiple agents, as tokens of a type. It is, rather, an end that participants in an activity are trying to achieve together. The contrast is very clear in rock-climbing: everyone scaling the rock has the goal of getting to the top, but they do not all *share* it in the sense at issue. Climbing *partners*, however, do share the goal of reaching the summit together. The distinction makes a difference for practical reasoning. If my climbing partner and I share the goal of climbing Donner Pass, then we are each committed to trying to get to the top as a duo. Accordingly, we plan and execute our climb by coordinating actions, *e.g.*, taking turns to lead and belay. Each of us participates in social action aimed at the shared goal of reaching the top together. In contrast, everyone who plans to climb Donner Pass has the *same* goal, in the sense that all plan to do the same thing. But this goal is not shared by all would-be climbers. We are not all trying to reach the top together. My partner and I aim to reach the top together, but whether or not any of the others also do so is not our concern. If their goals figure at all in our plans, it is only as a background condition, like inanimate objects or weather.

The rock-climbing example illustrates a general point. What distinguishes collaborative activities is that participants view their actions as contributing to a goal shared with other participants, with whose actions theirs are coordinated. The relation of *participation* mediates between groups and their members, resolving the practical problem of relating levels of social organization on a case-by-case basis. In this sense, the participatory relation is constructed in episodes of joint action. As groups may be members of groups, the consensus view allows for collaborative action with multiple levels of participation. It thus provides an integrative framework for study of experimenting communities.

The participation relation is an instrumental one. The instrumental schema outlines an alternative, non-dichotomous relation between epistemic standards and social dimensions of scientific practice. Rather than being identified or decoupled, epistemic standards specify the shared goal of collaborative scientific practices. This instrumental relation is quite familiar in philosophy of science. But it is typically conjoined with a highly idealized account of science's epistemic goal (significant truths, explanatory representation of the world, empirically adequate theories). Given such an idealized goal, features of scientific practice necessary or conducive to achieving it can be derived, and held up as epistemic standards for science (fruitfulness, accuracy, wide scope, etc.). However, there are few points of contact between these idealized goals and associated desiderata for theories, and collaborative experimental fields like stem cell research. Epistemic standards derived from idealized epistemic goals have no critical purchase on these experimental practices.

In the following sections, I derive an epistemic standard that does engage the experimental practices of stem cell research, as well as other experimental fields. This derivation rests on three assumptions:

(1) Minimal instrumentalism: scientific practices can be understood and evaluated in terms of 'fit' between shared goals and means taken to them by participants.

(2) Scientific practices have an epistemic goal, characteristics of which are specified by empirical study of science rather than philosophical presumptions.

(3) The epistemic goal of scientific practices is *shared* – seen by participants as something to be jointly achieved.

From these three premises, two requirements follow:

(A) The shared goal of a collaborative action is achievable by the group that has it.

(B) Means taken to the shared goal are coordinated among group members.[5]

These two requirements constrain the participatory relation in an instrumental framework presupposed in our familiar habits of explaining and evaluating human action. They thus indicate the form of the bridging relation needed to resolve the dilemma set out in the previous chapter: epistemic ideals are the shared goal of our scientific practices. In any particular case, the participatory relation will be specified so as to conform to the requirements, which are preconditions for there being a specifiable relation at all. Though thin, they are not trivial. But on their own they tell us little about science. To say more requires empirical study of scientific practices. And here I turn to stem cell research in particular.

Collaboration in stem cell research

Stem cell biology is a very young field with a long and intricate interdisciplinary history.[6] Stem cells in general are defined by two capacities, both having to do with results of cell division: self-renewal and multipotency. The first is the capacity to divide to produce indefinitely more cells

[5] More precisely: (A) If group G has shared goal S, then members of G (M1, M2…Mn) accept that it is possible for G to achieve S by some means ϕ (ϕ1, ϕ2,...ϕn), and that G has not actually done so; and (B) If members M1, M2…Mn take actions ϕ1, ϕ2,...ϕn as means to S, then they are committed to ϕ1, ϕ2,...ϕn being coordinated parts of G's plan to S, in accordance with standards for coordination accepted by G.

[6] Contributing fields include developmental biology, immunology, reproductive medicine, neuroscience, cancer biology, molecular genetics, and (most recently) systems biology. For a lively overview of stem cell research through 2005, see Fox (2006).

of the same type), while the second is the capacity to divide to produce more differentiated cell types. These more differentiated progeny make up the organs and tissues of a biological organism. So a stem cell, in general, is a self-renewing source for organismal development at the cellular level. There are four main types, distinguished in the first instance by developmental stage of the source organism: embryonic, fetal, adult, and induced. Adult stem cells are diverse, including 'source' cells for most major tissues and organs (neural, mesenchymal, cardiac, etc.). Induced stem cells are produced by human intervention; 'reprogrammed' adult somatic cells. A fifth type, cancer stem cells, remains hypothetical - the pathological counterpart of adult stem cells. [7]

Blood – or hematopoietic - stem cells (HSC for short) are adult stem cells, localized primarily to bone marrow, which differentiate to form the immune system. In organismal development, embryonic stem cells are primary, the beginning of developemental history. But in the development of stem cell science, it is HSC that are primary. HSC were the first stem cells isolated, and are currently the best understood, as well as the only stem cells routinely used in clinical practice (bone marrow transplantation).[8] As per usual, research on human stem cells was preceded by work in animal models – inbred mice and rats. So the stem of stem cell research, so to speak, was isolation and characterization of HSC in mice. This achievement provided the methodological model for research on other stem cell types (neural, cancer, germline, embryonic), and continues to influence the field.

To determine the role of collaborative interactions in this accomplishment, I used published sources, personal interviews, and laboratory visits to identify key interactions and

[7] Though currently the focus of many thriving research programs, the existence of cancer stem cells has been demonstrated to date only in leukemias.
[8] The role of HSC in the history of bone marrow transplantation therapy has been examined by Alison Kraft and colleagues (Kraft 2009, forthcoming; Martin et al 2008).

successes, from the field's emergence in the 1960s through four decades of advance. The resulting narrative is 'participant-driven,' in that the researchers involved identified both the significant collaborations and successful results. My role was to accommodate their diverse perspectives within a coherent, multi-level narrative, specifying the participatory relations that contributed to scientific success for research teams, laboratory groups, fields and sub-fields.

Here I discuss only the main results of this study.[9] Key successes in the HSC episode include: development of a functional assay demonstrating the existence of HSC (early 1960s); purification and characterization of these cells by surface phenotype, followed by isolation of neural and embryonic SC (late 1980s); elaboration of models of blood cell development (1990s); and, most recently, the cancer stem cell theory (2001). When collaborative interactions are emphasized, two robust components of these successes are revealed: construction of improved models of blood cell development, and formation of new boundaries among scientific groups.

These two components of success are interdependent. Consider, for example, the initial characterization of HSC. Since the early 1960s, attempts to identify this cell type had been organized around a focal method: the spleen colony assay. Developed at the Ontario Cancer Institute in Toronto, the spleen assay was an offshoot of radiation research on mouse bone marrow cells (Till and McCulloch 1961). In the 1950s, it was discovered that mice given lethal doses of γ-radiation can survive if injected with bone marrow cells from a donor of the same inbred strain. One side-effect of "radiation rescue" was the appearance of bumps, or nodules, on the spleens of transplant recipients. The Toronto group, investigating splenic nodules in the early 1960s, identified them as colonies of blood cells of various types: red blood cells, granulocytes, macrophages, and lymphocytes. Each nodule, however, was descended from a single donor bone marrow cell, and so comprised a clone or colony. Based on the spleen assay,

[9] For further details on methods and results, see Fagan 2007 and Fagan, in press.

HSC were operationally defined by the "capacity for generating cells assayable as spleen colony-forming cells" and, at least initially, identified with colony-forming cells (Metcalf et al 1979, 411). The number of spleen colonies formed after transplantation taken as a measure of HSC abundance in a given cell preparation.[10]

The quantitative spleen colony assay was the linchpin of the HSC research community, furnishing the nascent field at once with definite subject matter and a method of measurement. HSC were initially identified with colony-forming cells (CFC) in the Toronto spleen assay, modifications of which were soon developed in Melbourne (1966) and Manchester (1977). HSC researchers were mainly hematologists (medically trained experts on blood cells) with diverse research interests, which intersected on the search for the blood stem cell. The HSC community was organized around centers in Toronto, Manchester, Melbourne, New York (an offshoot of the Melbourne group), and Rijswijk - the last the site of an important Radiobiology Institute in the Netherlands, where the most striking progress in isolating HSC was made before 1988.

During the 1970s, the HSC community established forums for regular discussion. Some already existed: the International Society of Hematology, as well as local hematological societies in America, Asia and Europe, sponsored annual meetings, and the American Society of Hematology produced a weekly journal, *Blood*. HSC researchers contributed regularly, and one of the co-inventors of the spleen colony assay, Ernest McCulloch, served on *Blood*'s editorial board (1968-1980). A more specialized group, the Society for Hematology and Stem Cells, was formed in 1950 to discuss pre-clinical data.[11] In 1972, this group was incorporated as the International Society for Experimental Hematology, and instituted an annual meeting and

[10] It was unclear, at the time, whether CFU-s was a measure of the absolute number or relative frequency of HSC. Increased numbers of spleen colonies, relative to normal bone marrow, indicated degree of HSC 'enrichment' by a given method of concentrating HSC.

[11] 'About ISEH - History' (http://www.iseh.org/i4a/pages/index.cfm?pageid=3285).

monthly journal, *Experimental Hematology*. Other specialized journals soon followed: *Blood Cells* (1975-1995) and *Stem Cells* (1983-present).[12] Regular meetings and shared publication venues knit the diverse groups working on HSC into a community, facilitating comparison of work at widely-distributed sites in the Americas, Europe and Japan.

This experimenting community proceeded by division of labor: each group tried a somewhat different protocol for enriching HSC, and results were pooled and compared at regular meetings. The hematologists' steady progress in purifying HSC was interrupted in 1988 by the announcement that a group of Stanford immunologists – *not* part of the community seeking HSC - had isolated the cell (Spangrude et al 1988). Controversy immediately ensued. Over the next few months a new, expanded HSC community formed, which combined the approaches of developmental immunology and hematology. By the standards of this merged community, HSC was not yet isolated and characterized. However the Stanford group had made an important contribution. Their 1988 protocol implied a model of blood cell development that coordinated HSC capacities with cell surface phenotype, at the single-cell level. This provided a more detailed characterization of early stages of blood cell development than previous studies, which was readily extended to the search for human HSC.

These features count as improvement, of course, only in a community aimed at characterizing the stages of blood cell development in mammals and (especially) humans. The other component of the 1988 success was a synthesis of developmental and cellular immunology, which gave new direction and impetus to the field of HSC research. Controversy over the 1988 result was symptomatic of the 'collision' between different fields. Until that time, the Stanford group and the hematological HSC community were unaware of one another. The widely-

[12] The latter was succeeded in 1995 by a new journal, *Blood Cells, Molecules and Diseases*. The newest, and currently most influential, journal in this tradition is *Cell Stem Cell* (est. 2007), the official publication of the International Society for Stem Cell Research (ISSCR).

publicized *Science* paper connected previously distinct lines of inquiry. Controversy promptly ensued over their different methods and standards for isolating HSC. Consensus that HSC had not been isolated emerged concomitantly with the Stanford group's integration into the wider HSC community. Key members of each community "traveled to meetings around the world to explain our differences," and Stanford researchers deliberately "mend[ed] bridges with everyone in the field."[13] In the process, key criticisms came to light. The Stanford group accepted these criticisms, and took up the challenge of isolating HSC as part the new experimenting community with that aim.

Formation of the new group depended on announcement of the new model, which in turn counted as improved according to standards of that new group – and the search for HSC went on, as models of blood cell development grew more elaborate, and extended to other systems. This two-part pattern of success recurs throughout the history of blood stem cell research, at various levels of social organization. A 1997 controversy between two laboratory groups over incompatible models of blood cell development was eventually settled - not by showing that one group's result was incorrect, but by distinguishing between their aims. One (based in the US) was interested in cell signaling *in vitro*, the other (based in Kyoto) in fetal immune mechanisms. With resolution of the controversy, models of blood cell development were improved, in the sense that each was rendered consistent with available evidence. But this was accomplished by splitting, rather than merging, the two groups.[14]

The most recent success stemming from HSC is the theory that malignant tumors stem from a few cancer cells using the same molecular mechanisms as stem cells in normal organs and tissues – the cancer stem cell theory. Though not decisively confirmed, its unification of cancer

[13] Visser, quoted in Radetsky 1995; Spangrude (interview of 12/4/2006).
[14] The Kyoto group's model is currently accepted by the HSC community, whose goals prioritize physiological mechanisms and potential therapies over biochemical possibilities *per se*.

research with developmental biology and functional genomics is currently considered a success. The two-part pattern holds here as well. The unified model of normal and malignant development counts as improvement in the new interdisciplinary field, as basic researchers and clinicians collaborate in its testing and development. The two-part pattern of success is robust throughout the HSC episode, and plausibly also holds for other biomedical episodes, and for experimental sciences more generally.

Abstracting from the diverse experimental details, the empirical study of HSC research has three main results. First, construction of improved models is *coordinated with* formation of new group boundaries. This amounts to a general mechanism for successful experimental science: models constructed in one group context are given critical scrutiny from a new (though not wholly unrelated) perspective, as new group boundaries form. Second, this conception of scientific success approximates familiar epistemic values. Improved models are taken to increase the scope, consistency, precision or accuracy of our knowledge. Coordination of diverse lines of inquiry recalls epistemic virtues of consistency, coherence and unification. But these ties to epistemic ideals are rather abstract.

The third point is most significant. It emerges from considering the mechanism for scientific success in its context of operation; the social history of science. The pattern of group boundaries and improved models – the actual path of scientific success – depends in part on specific experimental results. For example, in original characterization of HSC, the experimental turning point was the convergence of three separate projects in the Stanford lab onto the same cell population, suggesting a common 'stem' for different blood cell lineages. This result put the Stanford group into the search for HSC, leading to the 1988 announcement, merger with the hematological community, and the methods and standards that prevail in SCB today. In the US-

Kyoto controversy, the experimental turning point was different performance of the same cell type in different functional assays. Without these conflicting results, there would have been no incompatible models, and the split into different sub-fields would not have occurred. For cancer stem cells, the key experimental result was similar gene regulation pathways in normal stem and tumor cells. Without this molecular parallel, the new interdisciplinary group of cancer researchers, developmental biologists and clinicians would not have formed, and the unifying cancer stem cell model would be no advance.

Collaborative derivation of an epistemic standard

In this decisive role for experimental results, my account meshes with epistemologies of experiment that take the epistemic standard for science to be reliable delineation of causal mechanisms by an experimental system.[15] My account goes beyond these, however, focusing on the collaborative interactions that link diverse experimental systems so as to constitute wider experimenting communities. It is these experimenting communities that produce knowledge in the form of models. For these communities, a further epistemic standard can be derived. This derivation specifies an epistemic ideal for collaborative scientific practices – an epistemic ideal for standards in practice.

The derivation follows the instrumental schema described above: given coordinated means taken in practice, what must the shared epistemic goal be like? To answer this question is to explicate an epistemic standard for collaborative scientific practices. Here the consensus view of collaborative action comes back into play. If scientific practices can be understood and evaluated in terms of instrumental rationality, then they have a shared goal that is achievable by

[15] See recent literature on mechanisms and causal explanation in experimental sciences (*e.g.*, Machamer et al 2000, Woodward 2002, Craver 2006, Darden 2006).

coordinated participant means. I assume this antecedent is true, and that the shared goal is epistemic (see above). The coordinated means are revealed by empirical study of collaboration in practice to have two parts: construction of improved models and formation of new group boundaries, The specifics of both – the particular groups involved and content of improved models - depend on experimental results. So the path taken by these coordinated means cannot be specified in advance of inquiry. But standards of improvement for new models depend on new boundaries. So the epistemic standards by which a successful model will be evaluated cannot be specified in advance of inquiry.

The shared epistemic goal of collaborative scientific practices is knowledge that could be achieved by these means – an epistemic product that could result from the continuing interplay of model-construction and boundary-formation – knowledge such as to satisfy epistemic standards not specifiable in advance. This rules out 'knowledge by agreement' as the shared epistemic goal. Knowledge that is so in virtue of the epistemic standards of specifiable groups in particular socio-historical contexts, is not an achievable shared goal, by the coordinated means of successful scientific inquiry. This result specifies an epistemic ideal for collaborative scientific practices. They aim at knowledge that satisfies epistemic standards not limited to any specifiable group. Such knowledge is 'objective' in a sense long associated with scientific inquiry: independent of the opinions of any single individual or group of individuals.

Summary and conclusion

I began with a minimal consensus on collaboration, grounded in social action theory. This minimal consensus provides a theoretical framework for studying scientific practices, which foregrounds participatory relations between shared goals and means of researchers. Within this

framework, empirical study of blood stem cell research yields a robust characterization of scientific success. The framework also entails two general requirements: preconditions for minimal instrumentalism. Combined with the robust characterization of scientific success, these preconditions are used to derive features of the shared epistemic goal of our collaborative practices. The result is a conception of scientific objectivity that is robustly grounded in scientific practice, but is *not* socially constructed in the sense of being constituted by our negotiations and agreements. Rather, this ideal of scientific objectivity is jointly specified by instrumental requirements for collaboration, commitment to decisive role for experiment in inquiry, and the robust results of socio-historical study of science. In this way, my account both explicates and enacts collaborative experimental inquiry, integrating different approach to scientific practice, rather than dividing them.

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FIGURE 1: A recent, simplified model of blood cell development (from Lensch 2006, archived in imagefiles of the International Society for Stem Cell Research).