

Stem Cell Research: Elephants in the Room

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When groups of stem cell researchers meet or when stem cell researchers publish their data and interpretations in scientific journals, a small cluster of important issues loom over the discussions yet often go unremarked. These issues influence much of the nature, direction, and funding of stem cell investigations, particularly those involving adult stem cells. The unmentionable issues are like the proverbial “elephants in the room”: large, impossible to ignore, and coyly disregarded by those with a habit or inclination to repress anxiety-inducing facts. As in psychotherapy or at family gatherings, ignoring the elephant is often the most comfortable option, but in the long run it is also counterproductive. In naming these metaphorical elephants directly, despite the anxiety often raised in doing so, they may be tamed, reduced, or even coaxed from the room.

The elephants discussed in this commentary are not the only stem cell–related elephants by any means, but they are the ones that I hear most clearly trumpeting their presence at scientific gatherings. Thus, this commentary is exceedingly personal—different investigators might take note of very different looming beasts. The topics that I have chosen to name include issues of scientific methods and socio-political situations that impact the science. I also focus on the “jungle” I know best, that of adult stem cells. There are other, often neighboring, jungles with their own distinct elephants.

I encourage all people interested in advancements within this exciting area—scientists, clinicians, ethicists, politicians, journalists, businessmen, and of course those who hope to benefit from stem cell therapeutics—to become familiar with these elephants. Familiarity makes it less likely that a person will inadvertently be stepped on. Moreover, being aware of some elephants may encourage people to remain on the lookout for others; elephants usually travel in large herds.

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Elephant No. 1: The Fall and Rise of Tissue Biology

The success of the biological sciences during the past centuries has largely arisen from the tendency to break the organism down into component parts. It has been a relatively steady march of progress: gross anatomy leading to histology, in turn leading to cell biology, and then to molecular biology. The success of this approach is obvious, but limitations are emerging at the frontier that stem cell research represents.

With the emergence and dominance of molecular biology, the nature of data and the manner in which data are acquired have changed. The introduction of gel electrophoresis, as well as measuring and demonstrating molecular processes within cells, became the hallmark of scientific data production and presentation. Microscopic images, when presented as data, usually show isolated cells in the culture dish. Even then, it is the molecular aspects of the presented work that predominate. When histological images, ie, pictures of tissue, appear in journals devoted to basic biological sciences, they are most often treated as opportunities for aesthetically pleasing covers, rather than the core scientific data of the report. The content of the journal articles typically addresses chemistry or biology within the gel or the cell, not in the tissue.

However, it is impossible to understand *in vivo* stem cell plasticity (Table 1) without considering tissue biology. The data of greatest import in this work have proved to be the histological images, not the isolated cells or molecules. Cell and molecular biology obviously play important roles, particularly in determining the mechanisms whereby cells of one tissue become those of another, but the final determination of experimental results is best and perhaps only demonstrated by creative staining and photography of the presences of cells *in tissues*.

Moreover, the tissue-specific functionality of cells that are completely incorporated into normal tissue architecture is often overlooked by cell and molecular biologists. In contrast, classic physiologists and pharmacologists often demand demonstration of function, even when tissue structure is provided as data. After decades of focus on cell culture methods, in which demonstration of function must exist outside of tissue structure, these cell and molecular

scientists have forgotten (if they ever knew) that maintenance of tissue architecture says more about functional status of a cell than any small set of functional markers they might suggest. After all, incorporation into and maintenance of tissue architecture *are* demonstrations of tissue-specific function.

Thus, stem cell research necessitates a reassembly of the component parts, with a reemergence of tissue biology as “basic science” and of the histological image as the most important unit of data. Although many stem cell investigators are thoroughly trained in the ways of cell and molecular biology, few have any but the most rudimentary training in normal microanatomy, let alone how that anatomy changes in the disease and injury models they use. Veterinary and medical anatomical pathologists have this training. It behooves stem cell investigators to collaborate with these scientists and clinicians. Moreover, journals to which such work has been submitted should have such experts available to properly assess it. Without the involvement of these specialists, the field is impoverished and its investigations questionable.

Elephant No. 2: Cell Isolation *Is* Cell Conditioning

In this era of dogma busting, there is one dogma that no one suggests needs revision. In the elegant formulation of Lewontin,¹ “the internal and external co-determine the cell.” This means that there is no cell function or differentiation state that is independent of its microenvironment, yet cell and molecular biologists routinely speak of cell isolation procedures as separate from conditioning (ie, the process by which cells are manipulated in culture after their isolation). These isolation procedures, however, are always conditioning steps—the distinction between isolation and conditioning is false and arbitrary.

We routinely take cells from their normal environments and pass them through isolation procedures, the impact of which is rarely understood, let alone investigated. Setting aside the extraordinary violence of isolating cells from intact tissues via mechanical and enzymatic tissue disaggregation, consider a relatively nonviolent isolation procedure, that of CD34⁺ circulating hematopoietic cells from the peripheral circulation. Venipuncture and exposing cells to turbulence and contact with low-temperature metal and plastic surfaces is followed by antibody binding for flow cytometric sorting. Each of these may have enormous impact on cell functioning. Although there are some data on the effects of turbulence,² cold,³ and exposure to nonbiologic surfaces,⁴ understanding of the function of CD34 is minimal⁵; therefore, we have no understanding of whether binding of anti-CD34 antibody to the cell is stimulatory, inhibitory, or neutral. Thus, even before formal experimentation has begun, the conditioning of the

Table 1. **Definitions of Some Technical Stem Cell Research Terms**

Cell plasticity	The potential of a somatic stem cell derived from one tissue to differentiate into mature cells of another tissue (ie, transdifferentiation capacity)
Clonal expansion	A population of cells descended from repeated cell divisions of one single original cell
Fusion	The process of hybrid cell formation. In the context of stem cell research, such a process has been shown to occur in vitro between an adult and embryonic stem cell resulting in the induction of “multipotency” from the embryonic to the tissue-specific adult stem cell. This process has been considered one possible mechanism of attaining transdifferentiation capacity (ie, stem cell plasticity)
Genomic plasticity	The potential of a specific cell genome to undergo epigenetic reprogramming that enables transdifferentiation

cell is under way, but we have little understanding of the nature of that conditioning.

At the logical extreme, this problem leads to an “uncertainty principle” to be applied to cell behavior: that any attempt to observe a cell necessarily disrupts the microenvironment and therefore the nature of the cell.⁶⁻⁸ Whether such “uncertainty” is a result of our technological limitations or is directly analogous to Heisenberg’s principle in quantum physics remains unclear, although the latter may be argued. At the minimum, however, the assumption that the isolated *ex vivo* cell is representative of the *in vivo* cell in its normal environment is at best presumptuous. We underestimate the importance of this issue to our peril, yet we do so routinely and casually. One initial response is to simply become cognizant of the language we use; we must avoid statements that suggest too strongly that the behavior of isolated cells in an experimental setting reflects back on the behavior of cells and environments from which they derive. The cells in our hands and in our laboratories are not the same as they were in the body.

Elephant No. 3: Basic vs Applied Science

Stem cell studies, typically discussed and revered as hypothesis-driven “basic science,” are at this stage often fundamentally about application rather than elucidation of biological mechanisms. One can see this in requests for applications for private or public funding of such research, let alone the responses to these applications. Hypotheses are nice, in fact necessary, but the attention-getting importance of the work is often not about a pure understanding of our physical nature but about direct development of therapeutic interventions.

There is a constant tension between “basic” and “applied” science in presentations at stem cell biology meet-

ings. Panel discussions and meeting rosters are often a mix of hypothesis-driven research and attempts to jump-start clinical interventions, and, as responses to hybrid pursuits, the arguments that surround the work are often confused, arising from unstated differences in goals. One group of researchers might be caught up with details of which cells in the bone marrow can become cells of lung or liver tissue; another group grumbles about the “pointlessness” of the issue because whole bone marrow can probably “work just as well” as a particular subtype of progenitor. Enthusiasm for detail and impatience can flip back and forth across an audience as presentations proceed.

A current example of this can be found in the adult stem cell controversy about cell fusion (Table 1) and what it means to stem cell plasticity studies. The importance of the finding and its ability to generate discomfort depend completely on one’s point of view. To those who are simply interested in elucidating biological mechanisms of cell plasticity, purely for their own sake, there is no controversy, there is simply another mechanism of genomic plasticity (Table 1) to explore. To those who are therapeutically minded, the response depends on their cell of choice. If one is looking to induce maturation of hepatocytes from fetal liver cells or from embryonic stem cells, then fusion is a polemical thrust at the potential of adult marrow-derived cells. In contrast, if one is committed to developing interventions based on adult, perhaps marrow-derived, stem/progenitor cells, then this fusion research simply suggests another physiological process that can be manipulated for the desired purposes. The passions stirred by discussions of these findings clearly are not simply about the “facts” but about the investigational and practical goals of the individual investigator.

The situation is potentially further complicated by entrepreneurial pressures. At least in the United States, therapies and other practical benefits from cell manipulations are patentable and therefore potentially profitable. However, creating a patent based on such discoveries requires that the information not be disclosed in the public domain. The obvious impact is that scientists who have practical goals for their investigations, even if they are not “business-savvy,” are likely to be sought out by those who are business-savvy (from university offices of industrial liaison to private entrepreneurs to established industrial entities) within a short time. Subsequently, they often find themselves pressured to plan announcements of findings around business requirements or even to withhold data, undermining the free flow of ideas.

Of course, these tensions are not limited to the world of stem cells, but there are few areas more thoroughly infiltrated by them. Changes in investigational work have been developing for several decades, driven in part by altruism

but also by investment possibilities: first for the development of new drugs and subsequently for biological “products” of diverse types, whether for industrial purposes or for therapeutics. With rising pressures to benefit from or to cooperate with industrial/business interests, if only to secure readily available sources of funding when public funds might be scarce, the goals of the biologist change, sometimes subtly, sometimes to a great degree.

Thus, with or without the intrusion of entrepreneurial ambitions, basic scientists now often find themselves doing what might conventionally be characterized as applied science, and conversely applied scientists (ie, clinicians and engineers) suddenly find themselves doing basic science. Each of us probably has some fundamental, core professional identity that we use to present ourselves to the world: cell or molecular biologist, pathologist, surgeon, internist, etc. However, in reality, nearly all stem cell investigators have evolved (or mutated) into some combination of scientist, engineer, and entrepreneur (also politician—see Elephant No. 5, subsequently).

Elephant No. 4: *Nature*, *The New York Times*, and *The National Enquirer*

The influence of the media in the development of the stem cell field is as prominent as in any other segment of our culture. However, except for war, few other current topics have such a broad spectrum of coverage as stem cells, beginning with the scientific journals; moving through the general lay press, including television, radio, and print media; into specialized media, in particular those representing or catering to business concerns.

The reason for the widespread influence is obvious: stem cells have been hyped as the most recent best hope for a comprehensive cure-all for human disease, injury, and aging. Is there anyone without an interest in these possibilities? Many researchers in the field have already been through at least one round of press releases from their home institution or from the scientific journal publishing their work. These announcements are rarely ignored; rather, they are often followed by national and even international media attention. Eventually, these investigators will be on the list of “experts” interviewed for comments when other investigators’ work begins the same cycle of media exposure.

For the scientific journals that publish reports on stem cells, impact factors are maintained or increased with the announcement of new “high-profile” research. This is true for journals with high impact factors and for journals with lower impact factors. Indeed, stem cell research in general and adult stem cell research in particular probably afford the publishing journal the highest possible guaranteed exposure. The “impact value” was high for the earliest dem-

onstrations of adult stem cell plasticity, which leapt to particular prominence when the political debates surrounding funding of embryonic stem cell research flowed over the quieter work being performed (see Elephant No. 5). It continues now with each “cure” within an animal model of a terrible human disease: myocardial infarction, diabetes, multiple sclerosis, etc.⁹⁻¹¹

How does this impact the science? Journalism, including that reporting on the best of the scientific journals, increasingly relies on short, uncomplicated phrases—sound bites—to convey simple messages regarding any topic of high public interest. Thus, the complex data and early attempts at building integrative hypotheses, which are the hallmark of cutting edge research, often become oversimplified in the quest for rapid diffusion and for explanations “simple enough” for the general population.¹²

Indeed, it is not uncommon for scientists to find that complex statements are often chopped into inaccurate sentence fragments that, with quote marks, are read by family, friends, neighbors, colleagues, politicians, and people with serious, sometimes potentially fatal illnesses. Responses to these fragments, whether fair encapsulations or gross distortions of complex findings, then distort the debate. Moreover, many of the journalists at wide-impact newspapers have their set panels of commentators and interpreters; thus, journalistic commentary is often repetitively shaped by limited, perhaps even nonrepresentative, “experts” giving rise to further distortions, leading to subtle bias that remains unnoticed by the target audiences.

These processes would remain of only mild interest, perhaps worthy of minor gossip, if they were not played out in numerous ways in the lives of the people who follow the media for news on stem cell research. For example, interest of businesses and entrepreneurs is often first piqued and influenced by media representations of the field, rather than by the work itself. *The Wall Street Journal*, network evening news, and *Business Week* are among the first conduits to enhance potential investors’ awareness of new developments and possible business opportunities. The general public, made up of diverse interests but clustered around disease entities, does not generally read the primary report, but responds to media representations, contacting the investigators, their own physicians, or their advocacy organizations. Increasingly, this creates a practical and political pressure that feeds back into funding and research priorities.

Then, of course, there is the personal experience of the researchers now exposed to media scrutiny or co-opted by the media for its own purposes. This path may lead to 15 (or 50 or 500) minutes of fame for the researcher. Even if a researcher eschews such temporary celebrity, it is not without import for deans of institutions and for their departmen-

tal chairs. The time diverted by these pursuits can interfere with the work itself. Research agendas can be shaped by the utility of and craving for such media attention.

On the negative side of this arrangement, the tendency of the media to trade in or cater to simplistic versions of the complex truth can distort the production of data, open discussion of hypotheses, and dissemination of new findings. On the positive side, there is tremendous opportunity to educate the general public about exciting new developments and about the role that state-of-the-art science can play in the realm of the personal and of the public.

Elephant No. 5: The Embryonic vs Adult Stem Cell Debate

This is the biggest elephant by far. It has conditioned research agendas, funding patterns, and publication or rejection of data, ie, every aspect of and the scientific discourse around new findings. Some of the influence has been positive; much has been negative.

The initial reports of adult stem cell plasticity—blood to muscle, brain to blood, blood to liver¹³⁻¹⁵—were heralded by *Science* as the “scientific breakthroughs of 1999.”¹⁶ Naturally, the reports were immediately controversial. Chipping at decades-old encrustations of dogma, the revolutionaries were having a field day, while the dogmatists and guardians of doctrine were soon beside themselves. All in all, this activity occurred during an exciting but essentially normal time in the world of science, emblematic of the passionate engagement that is the best of science and the best of scientists. It was not certain whether the aforementioned 3 reports, and the rapid follow-up studies, would survive the test of time; but it was clear that this was more than a single laboratory reporting “cold fusion.”

Alas, it was around this time that the controversy about the use of embryonic stem cells flared. The first influence of this simultaneity was felt in the “meaning” attached to adult stem cell research. Immediately, the single most important feature of the research was that it could be used for therapeutic purposes. All subsequent funding applications, nearly all the research, and all the scientific editorializing would swirl around the practical applications of the findings, not about the “pure” science of finding out how our bodies work. From this moment forward, research into adult stem cell plasticity would always be looked at, first and foremost, through the lens of therapeutic applicability, rather than simple curiosity about the body. Thus, one might consider that this elephant was perhaps the mother of Elephant No. 3.

Worse yet, the study of adult stem cells became inextricably tangled with that of embryonic stem cells. A similar political engagement in biomedical research flared in the

mid-1990s with debates about use of fetal tissues; the political shift in America that followed the 1998-1999 change in American government created the chance for the anti-abortion lobby of the United States to exert greater influence than before. At some point early on in the embryonic stem cell debate, the antiabortion lobby seized on a potent, very simple formula: if adult stem cells could do everything embryonic stem cells could do, then embryonic cell research is not necessary.¹⁷ Our own report that a single transplanted marrow stem cell could, through clonal expansion (Table 1), generate tissues of mesodermal, endodermal, and ectodermal lineages was seized quickly by the antiabortion lobby as confirmation of this formula.¹⁸

The appropriately honest and accurate response to the false statement that, if adult stem cells could do everything embryonic stem cells can do, then embryonic stem cell research is unnecessary would be that the issue is not a simple "either/or"¹⁹ but instead is more complicated: maximizing the therapeutic potential of either cell population inevitably would require studying both cell populations. Information for making use of one cell population would inevitably be provided by studying the other, and furthermore it was entirely premature to predict which cell population would ultimately produce the most cost-effective therapeutic options.

However, the response of the proembryonic stem cell lobby, including scientists, journalists, and politicians, was swift, unequivocal, and unfortunate. Instead of attempting to convey a more complex message, they largely accepted these overly simplistic terms of the debate, responding in kind: embryonic stem cell research must go forward because adult stem cell research is not convincing. Thus, we have evolved to the current state in which support of embryonic stem cell research now requires that adult stem cell plasticity be repeatedly cast in a negative light.

Evidence for this can be found in a series of articles showing negative results published in high-quality journals.²⁰⁻²³ Although publication of negative results is crucial to the advancement of science, each of these prominent articles then had to face its own significant methodological criticisms of the sort that should have been addressed in the original process of review and acceptance.²⁴⁻²⁷ Particularly, they all shared an appearance of directly replicating prior research; however, in fact they made large and small changes in experimental design that made the experiments essentially incomparable to those in the earlier articles showing positive results. Indeed, one group of authors, when faced with those discrepancies of study design,²⁷ essentially retreated from the originally overstated claims for the negative result.²⁸

Thus, we have a decidedly uncomfortable situation. Few, if any, adult stem cell researchers object to embry-

onic stem cell research, yet they find their own work uncomfortably twisted by the antiabortion lobby to suggest that embryonic work is unnecessary. In contrast, after having accepted the false "either/or" terms of the debate thrust on them by antiabortion lobbyists, proponents of embryonic stem cell research find it necessary to undermine adult stem cell efforts. We are all in an unexpected and surprising bind in which political and social issues work not only to suppress lines of investigation but also to create internal conflicts for the scientists beyond more typical external conflicts. How this situation will resolve itself is unclear. The tensions, however, will certainly intensify.²⁹

Summary

The degree to which these elephants are disruptive to the steady advancement of the adult stem cell field will become clear with time. In some ways they enliven the discourse, but in many ways they interfere with efficient progress. Naming these elephants is a first step toward dealing with them. If we remain aware of these issues when evaluating new research, we are less likely to make careless mistakes, and we are more likely to be able to hold scientists, politicians, journalists, and entrepreneurs accountable for their practices. Although all adult stem cell researchers will spend time profitably riding some of these elephants, we will all inevitably spend more time cleaning up after them. Perhaps open, careful, and unbiased discussions of these elephants will help the cleanup work be less odious and completed sooner, rather than later.

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