

Stem Cell Research: Elephants in the Room

By Neil D. Theise

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- Liver Pathology, adult stem cell research, complexity theory, consciousness studies, human hepatocarcinogenesis
- Identification of liver stem cell niches and the marrow-to-liver regeneration pathway
- Pioneer of multi-organ adult stem cell plasticity and has published on that topic in Science, Nature, and Cell
- Current laboratory investigations focus on
 - nerve-stem cell interactions in human livers
 - melatonin-related physiology of human liver stem cell and regenerative processes
 - aspects of human liver stem cell activation in acute, fulminant hepatic failure
- Senior student of Zen Buddhism at the Village Zendo, New York City

SELECTED PUBLICATIONS

Krause DS*, These ND*, Collector MI, Henegariu O, Hwang S, Gardner R, Neutzel S, Sharkis SJ. Multi-organ, multi-lineage engraftment by a single bone marrow-derived stem cell. *Cell* 2001; 105: 369-377. (*contributed equally)

adult bone marrow cells have tremendous differentiative capacity as they can also differentiate into epithelial cells of the liver, lung, GI tract, and skin

These ND, Wilmot I. Cell plasticity: flexible arrangement. *Nature* 2003; 425: 21.

differentiation as an actively maintained, dynamic state rather than a one-way street explained by the action of irreversible gene restrictions

These ND. Cell doctrine: now you see it, now you don't. *Nature* 2005; 435: 1165.

Complexity theory: modern biology and medicine see the cell as the fundamental building block of living organisms, but this concept breaks down at different perspectives and scales (ant colony - individual ants - myriad cells)

These ND. The stem cell niche and tissue biology. *Stem Cell Reviews* 2007; 2: 169-70.

Zhang L*, These ND*, Chua M, Reid LM. The stem cell niche of human livers: symmetry between regeneration and development. *Hepatology* 2008; 48: 1598-607 (*contributed equally).

Bushell WC, Spector NH, These ND. From the global to the local: Possible pathways for the transduction of Indo-Sino-Tibetan cognitive-behavioral practices into site specific, tissue regenerative effects. *Ann N Y Acad Sci.* 2009; 1172: 74-87.

‘Elephant in the room’ or ‘Elephant in the living room’
English metaphorical idiom for

- something that is difficult or unpleasant to deal with
- an obvious truth that is going unaddressed
- an obvious problem or risk no one wants to discuss

It is based on the idea/thought that an elephant in a room would be impossible to overlook

Origin of the term

Fable "*The Inquisitive Man*" by Ivan A. Krylov (1814),
Russian poet and fabulist

*Story of a man who goes to a museum and
notices all sorts of tiny things, but fails to
notice an elephant*



"Barely Legal", Banksy art exhibition, Los Angeles, 2006
The exhibition featured this live "elephant in a room", which - according to leaflets handed out at the exhibition - was intended to draw attention to the issue of world poverty



No. 1: The Fall and Rise of Tissue Biology

Tendency to break the organism down into component parts

- gross anatomy
- histology, leading to
- cell biology
- molecular biology

The success of this approach is obvious, but limitations are emerging at the frontier that stem cell research represents

Hallmarks of scientific data production and presentation

- Predominance of gel electrophoresis data
- Measurement and demonstration of molecular processes within cells

Microscopic images, when presented as data, usually show isolated cells in the culture dish molecular aspects predominate

Histological images, ie, pictures of tissue, are most often treated as opportunities for aesthetically pleasing covers, rather than the core scientific data of the report

It is impossible to understand *in vivo* stem cell plasticity without considering tissue biology



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



No. 2: Cell Isolation *Is* Cell Conditioning

- No cell function or differentiation state is independent of its microenvironment
- Cell and molecular biologists routinely speak of cell *isolation* procedures as separate from *conditioning*
- Isolation procedures are always conditioning steps
- Distinction between isolation and conditioning is false and arbitrary

Possible **impact on cell functioning** by

- Cell isolation from intact tissues via mechanical and enzymatic tissue disaggregation
- Isolation procedure of CD34+ circulating hematopoietic cells from the peripheral circulation (venipuncture, exposure of cells to turbulence, contact with low-temperature metal and plastic surfaces, antibody binding for flow cytometric sorting)

“uncertainty principle” applied to cell behaviour

- any attempt to observe a cell necessarily disrupts the microenvironment and therefore the nature of the cell
- “uncertainty” is a result of
our technological limitations ?
directly analogous to Heisenberg's principle in quantum physics ?
- assumption that the isolated *ex vivo* cell is representative of the *in vivo* cell in its normal environment is at best presumptuous
- importance of this issue is underestimated, but done so routinely and casually
- 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



No. 3: Basic vs Applied Science

- Tension between “basic” and “applied” science
- Research funding in favor of the development of therapeutic interventions and less of pure understanding of our physical nature
- Confusion of arguments due to ‘hybrid pursuits’, ie, mix of hypothesis-driven research and attempts to jump-start clinical interventions, arising from unstated differences in goals
- Patent issue – scientists are pressured to plan announcements of findings around business requirements or even to withhold data, undermining the free flow of ideas
- Basic scientists find themselves doing applied science, and conversely applied scientists (ie, clinicians and engineers) suddenly find themselves doing basic science
- In reality, all stem cell investigators have evolved (or mutated) into some combination of scientist, engineer, and entrepreneur



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

Influence of the media in the development of the stem cell field

Stem cells have been hyped as the most recent best hope for a comprehensive cure-all for human disease, injury, and aging

Press releases are often followed by national and even international media attention → investigators are put on the list of “experts”

Complex statements are often chopped into inaccurate sentence fragments

Negative side: 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

Positive side: 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



No. 5: The Embryonic vs Adult Stem Cell Debate

- Biggest elephant
- Influences research agendas, funding patterns, and publication or rejection of data
- Initial reports of adult stem cell plasticity—blood to muscle, brain to blood, blood to liver — heralded by Science as the “scientific breakthroughs of 1999
- Around this time that the controversy about the use of embryonic stem cells flared
- Research into adult stem cell plasticity for therapeutic applicability (Elephant No. 5. is perhaps the mother of Elephant No. 3 — pure science versus application)

- US antiabortion lobby's simple formula: *if adult stem cells could do everything embryonic stem cells could do, then embryonic cell research is not necessary*
- Response of pro-embryonic stem cell lobby, including scientists, journalists, and politicians: *embryonic stem cell research must go forward because adult stem cell research is not convincing*
- Negative results published in high-quality journals, but changes in experimental design that made the experiments essentially incomparable to those in the earlier articles showing positive results

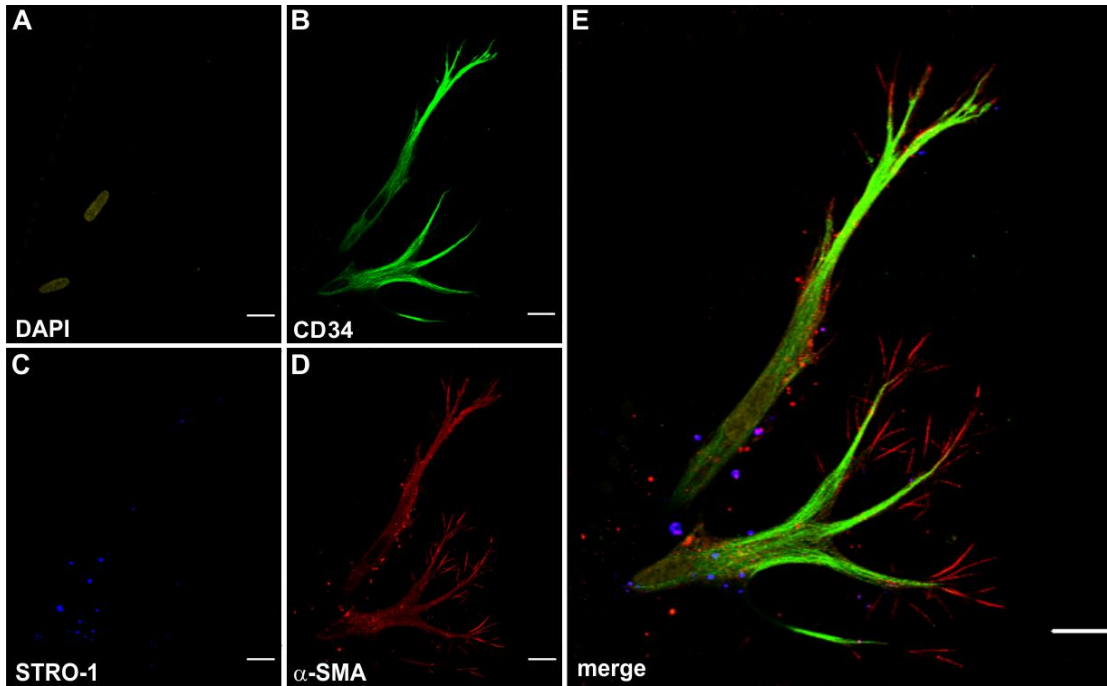
Summary

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

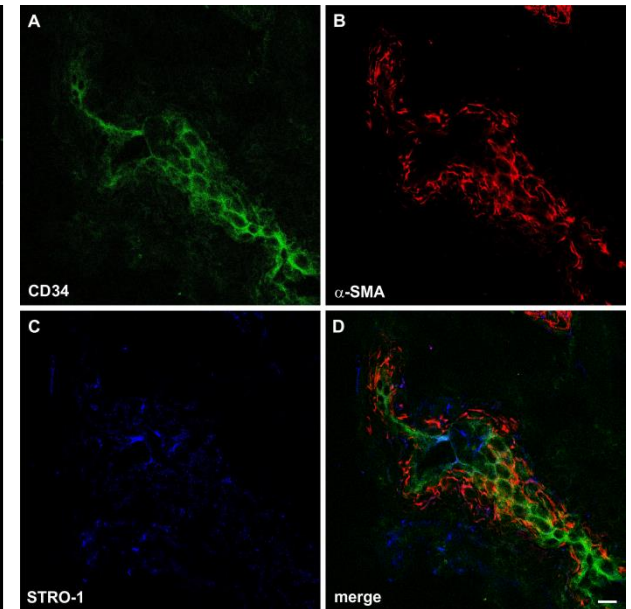




No. 1: The Fall and Rise of Tissue Biology



In vitro explant culture



Ex vivo tissue section