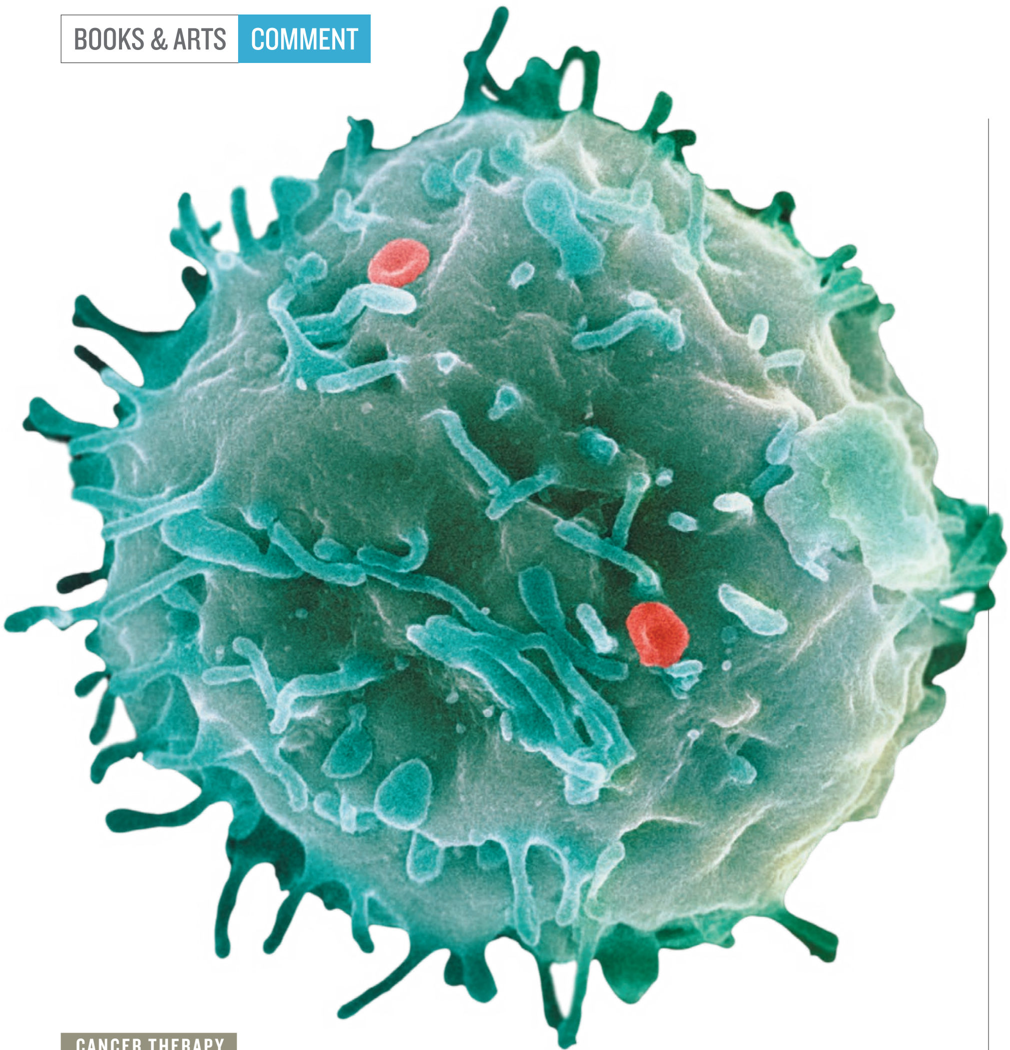


A stem cell seen under a scanning electron microscope.

SPL

CANCER THERAPY

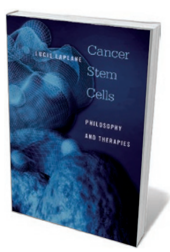
Defining stemness

Hans Clevers admires an analysis of stem-cell science that sharpens up some of the fuzziness in the field.

I have always felt uncomfortable about the concepts and definitions that we use in the stem-cell field. Some of the arguments seem circular; observation and assumption are not well separated. I once asked a colleague for their best definition of a stem cell. The answer: a cell that can self-renew. What, then, is self-renewal? The immediate reply: what stem cells do.

Fuzziness in stem-cell concepts and definitions has significant consequences. It affects how we design, conduct and interpret experiments, how we communicate our discoveries and, ultimately, how we design therapies aimed at supporting the regenerative capacity of healthy stem cells or eradicating those that fuel the growth of tumours. Despite these concerns, as an experimentalist I could never put my finger on where exactly scientific common sense is failing.

Enter Lucie Laplane and her book *Cancer Stem Cells*. Trained as a science philosopher, Laplane also spent time at the bench in two stem-cell labs. Her book is the culmination of a six-year effort to describe and structure the philosophical underpinnings of stem-cell science. In addition to absorbing essentially all the relevant experimental literature — historical and scientific — she interviewed some of the leading international stem-cell researchers and clinicians. She discussed her emerging insights with fellow philosophers and science historians. Starting from an interest in cancer stem cells (CSCs), the book, despite its title, builds a much broader framework for understanding the biology of stem cells of all types.



Cancer Stem Cells: Philosophy and Therapies
LUCIE LAPLANE
Harvard University Press: 2016.

Central to CSC theory is the observation that not all tumour cells are equal. The bulk of a tumour consists of short-lived proliferative cells and differentiated cells. But some tumour cells seem to be the malignant equivalents of tissue stem cells. Much as normal stem cells maintain healthy organs by producing new tissue cells, CSCs drive the persistence of malignant tumours by producing new cancer cells.

CSC theory tacitly assumes that CSCs carry the armaments of normal stem cells: they are built to last a lifetime; are resilient to many kinds of chemical or physical insult; and can 'slumber' for prolonged periods. CSCs would thus be capable of surviving chemotherapy and radiation, explaining why local recurrence is the almost inevitable outcome of such treatment. And metastases that sometimes appear many years after the excision of a primary tumour would be caused by quiescent CSCs that have wandered to distant sites. Thus, CSC theory explains why cancer patients can never be considered cured, even when a treatment outcome seems encouraging. Most important, CSC theory promises the development of innovative treatments, aimed not at reducing the bulk of a tumour, but at taking out its 'beating heart': the cancer stem cells.

Laplane starts her comprehensive overview with a description of how the popularity of CSC theory has exploded over the past two decades, driven by the rapid development in cell-sorting technology. She then gives an insightful historical account starting from nineteenth-century giants including Theodor Schwann and Rudolf Virchow. Almost as an aside, she describes the work of Leroy Stevens and Barry Pierce on transplantation of cells from teratocarcinomas, eerie growths that can contain any type of tissue, including teeth and hair. This eventually led to the discovery and 'domestication' of their healthy physiological counterparts, the embryonic stem cells that generate all tissue types in early embryos.

She discusses, too, how Canadian stem-cell biologist John Dick revived the field in the 1990s by developing ways to study the behaviour of different types of human leukaemia cell by transplanting them into mice. He merged this with modern insights into the nature of the healthy stem cells that give rise to all types of blood cell (haematopoietic stem cells). He discovered that within a patient, a minority of leukaemia cells closely resemble healthy stem cells, but

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rather than producing normal blood cells, they continuously produce leukaemia cells. Thus, Laplane concludes that the definition and study of CSCs is inseparable from that of normal stem cells.

Laplane defines a stem cell as one "capable of self-renewal and of differentiation", where self-renewal is the ability to recreate one copy of itself on division. Laplane reveals how for some time the field was describing two very different entities as CSCs: the cells from which tumours originate; and those inside tumours that drive their growth in the long term. Apples and oranges. The field has also wrestled with the gold-standard assay introduced by Dick: the transplantation of sorted human cancer cells into mice, where the cells that grow out into tumours are considered CSCs. It is arguable what this 'surrogate' assay actually measures. Does the outgrowth of heavily manipulated cancer cells in mice really reflect the behaviour of the same cells in the original tumour? Laplane acknowledges these issues. In a second edition, she may want to touch on how researchers use genetic marking of stem cells to trace their derivatives through solid tissues.

"Fuzziness in stem-cell concepts has significant consequences, but I could never put my finger on where scientific common sense is failing."

Laplane's rigorous analyses unveil deep semantic and conceptual problems in the field. She arrives at a framework of four possible versions of 'stemness': two intrinsic, two extrinsic. She suggests that it can be categorical (an intrinsic property of a stem cell, independent of its environment); dispositional (an intrinsic property of a stem cell that emerges only in the right environment); relational (an extrinsic property induced in a cell that would otherwise be a non-stem cell by its microenvironment); or systemic (an extrinsic property of a system such as tissue, rather than an individual cell).

I suspect that there is no current consensus on where to fit even the best-studied stem-cell types into this framework. Yet Laplane's stemness framework should be of great value. It will help to clarify definitions and concepts, even if it only provides solid ground from which to disagree. Moreover, the framework can readily be applied to experimentation. A philosopher may indeed have straightened out the stem-cell field. ■

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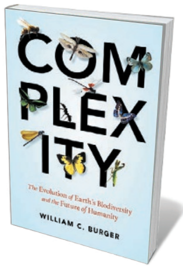
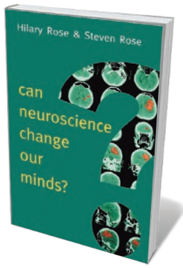
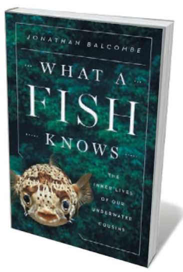
Books in brief



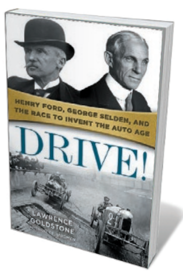
Complexity: The Evolution of Earth's Biodiversity and the Future of Humanity
William C. Burger PROMETHEUS *(2016)*
Botanist William Burger conducts a grand tour of life's complexity, emphasizing cooperation and symbiosis in evolutionary history. He segues deftly from the towering success of beetles and bacteria to the formation of new species and the distribution of biodiversity. The story culminates with humanity's cognitive and cultural hegemony. But however ascendant we are as a species, Burger dispassionately notes, our explosive global population growth and overuse of resources mirror the behaviour of locust swarms.



Can Neuroscience Change Our Minds?
Hilary Rose and Steven Rose POLITY *(2016)*
The seepage of neuroscience into economics and policy should be deeply questioned, argue sociologist of science Hilary Rose and neuroscientist Steven Rose in this crisp, astringent analysis. In a historically and scientifically contextualized critique of this "data-rich and theory-poor" discipline, they examine claims made for the US and European 'big brain' projects, and for the findings that feed into UK policy on child-rearing and early education. Ultimately, they aver, neuroscience can indeed change our minds — but social and political understanding of the issues must be factored in.



What a Fish Knows: The Inner Lives of Our Underwater Cousins
Jonathan Balcombe FARRAR, STRAUS AND GIROUX *(2016)*
More than 30,000 species of fish — about half of all vertebrates — roam global waters. And as ethologist Jonathan Balcombe notes in this engrossing study, breakthroughs are revealing sophisticated piscine behaviours. Balcombe glides from perception and cognition to tool use, pausing at marvels such as ocular migration in flounders and the capacity of the frillfin goby (*Bathygobius soporator*) to memorize the topography of the intertidal zone. Yet, he argues, the over-exploitation of wild stocks, notably of apex predators such as tuna, points to the need for change on moral as well as ecological grounds.



Drive! Henry Ford, George Selden, and the Race to Invent the Auto Age
Lawrence Goldstone BALLANTINE (2016)
Historian Lawrence Goldstone follows the momentous patent war that ended in 1911, when George Selden's case for a patent on a "road carriage" powered by internal combustion was broken by arch-industrialist Henry Ford, who adapted existing technology to craft the wildly successful Model T. Goldstone weaves in accounts of European innovators such as Karl Benz, and road races such as the 1907 Peking-to-Paris dash. But as the market-savvy maverick who "did not so much create demand as anticipate it", Ford dominates the story.

Silent Sparks: The Wondrous World of Fireflies
Sara Lewis PRINCETON UNIVERSITY PRESS *(2016)*
The pulsing glow of massed fireflies is a nocturnal wonder of nature. Biologist Sara Lewis has spent decades studying these beetles of the family Lampyridae, which spans nearly 2,000 species. Here she expounds on firefly metamorphosis, courtship, reproduction and bioluminescence — from the exquisite anatomy of the *Photinus* firefly's lantern to the chemical 'light switch' that enables flash control. (A field guide to North American fireflies is included.) An illuminating peek into a fascinating corner of field biology. **Barbara Kiser**