



BOOK REVIEW

Songs in the Key of Life

Adrian Woolfson*

In his new book, Siddhartha Mukherjee, the author of two modern classics—*The Emperor of All Maladies* and *The Gene*—writes elegantly and candidly about the promise of cellular therapy and his hopes for “a new kind of medicine.”

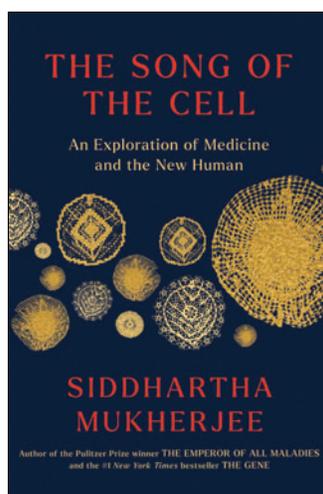
If a population of cancer cells were able to sing, their songs would be more likely to resemble the unsettling cacophony of the German composer Karlheinz Stockhausen's seminal composition *Gesang der Jungline* than the sublime harmony of a Welsh male voice choir. Except of course, not everyone would agree with this unfavorable assessment of the alien-sounding combination of erratic schoolboy chants and electronic whines from which its score, conceived in 1956, is contrived.

For some, Stockhausen's idiosyncratic aesthetic, and the synthetic “new music” he created—as definitively separated from the established Western and Eastern canon, as the paintings of Kandinsky are from those of Titian—represented a welcome and visionary deviation from the banality of historic musical form. He single-handedly metamorphosized musical form into a new realm of synthetic mystery.

Although doubtless an enigmatic genius, Stockhausen has also been unkindly described as “a pseudo-intellectual hippymystic with a liberating gift for creating utter nonsense.” Regardless, his work represented the beachhead of a pioneering avant-garde movement that propelled musical structure into uncharted territories. His remarkable contribution to contemporary music was celebrated by his inclusion in the iconic *Sergeant Pepper* album cover, accompanied by Marlon Brando and Marilyn Monroe.

In his thoughtful and optimistic new book *The Song of the Cell*, often sparkling with poetic and insightful metaphors, the physician-scientist, clinical investigator, entrepreneur, and Pulitzer Prize-winning author Siddhartha Mukherjee outlines a synthetic cellular manifesto for “emancipating humans from the ravages of diseases” and for generating what he refers to as “new humans” and “newer humans.”

Although the boundaries of these are, perhaps necessarily, poorly defined, Mukherjee makes it clear that his vision for humankind's future is firmly anchored in human nature, as we currently know it. So while aspiring to eliminate all human maladies, his sweet spot for doing so appears to reside within



The Song of the Cell

by Siddhartha Mukherjee
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the more conventional region of a spectrum that accommodates both the human nature equivalents of the chaotic unfamiliarity of Stockhausen's “new music” and the more anodyne familiarity of The Beatles.

The book comprises a compelling popular account of the important and rapidly evolving science of cell therapy, which Mukherjee describes as “a new kind of medicine,” interweaving some personal vulnerabilities with his experiences of treating patients with cancer and other blood diseases. It also details the thrill of translating scientific discoveries—some of which are his own—into new medicines. “[It is] hard to describe the mix of terror, anticipation and exhilaration that you experience when a discovery from your lab makes the transition into a human medicine,” he writes.

Mukherjee's enthusiasm for his work is viscerally palpable, such as when he describes how while examining a patient's blood smear under a microscope, he ran his eyes through it “like a wild animal sensing a new landscape.” He honors the unsung heroes of “the jagged record of failure”—the many patients who lost their lives helping to evaluate failed medicines that have nevertheless provided important insights that might one day benefit others. His infectious energy leaves us in no doubt that he is on a personal mission to put a “pox on cancer,” and to permanently destroy its malignant song.

Although literary, entertaining, and pitched perfectly for a popular audience, one is left with the feeling that key issues, including the formal definition of a “new human” and potential utility of this concept, are passed over in a rather perfunctory manner. At one point, it appears as if the definition may be broad enough to encompass patients treated with cell transplants. It might even include those that have been administered immune system-manipulating monoclonal antibodies such as the anti-PD1 and anti-CTLA4 checkpoint inhibitors, which Mukherjee eloquently describes as making cells “re-visible to the immune system.”

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Siddhartha Mukherjee (Credit: Deborah Feingold)

This type of overinclusive definition would make the concept redundant, as it is hard to see, for example, how a sickle cell or beta thalassemia patient, whose genome has been edited to boost the levels of fetal hemoglobin, or a diabetic transplanted with iPSC-derived insulin-secreting beta cells, could be perceived as being a “new” or even a “newer” human. Neither would such individuals be different enough to be referred to as new “kinds” of humans. Indeed, the use of such terms in this context could be perceived as being unnecessary, stigmatizing, and divisive.

Of course, there is a point at which a difference in amount becomes a difference in kind. There is likely an as-yet-to-be defined threshold, beyond which one could argue that a “new kind of human” had been generated. But I doubt whether patients wish to be considered in this way, and whether they would be able to cross that threshold, even in principle, with the types of cellular interventions Mukherjee anticipates.

Important philosophical issues, including how we go about delineating the boundaries of human nature, the way in which conflicting constraints between phenotypic features and the interconnectivity of gene networks invariably limit the possibility of optimizing characteristics in one dimension without compromising others, and ethical considerations including the types of interventions that might be considered acceptable or desirable, are similarly given short shrift. Although providing a detailed and appropriately critical analysis of He Jiankui’s unethical and ill-informed editing of the human germline, Mukherjee states that “the genetic manipulation of the human embryo to arrest diseases (or perhaps even to enhance human abilities) seems, every day to become an inevitable destination of medicine.” But he does not make it clear whether he is referencing somatic or germline editing, or indeed whether he endorses it, and if so, to what extent.

This appears also to be at odds with his somewhat obscure definition of a “new human” as being “a human rebuilt anew with modified cells who looks and feels (mostly) like you and

me.” The author asserts that the “borderline between ailment and enhancement blur.” “Newer humans,” as he calls them, appear to be the result of a more extreme form of cellular modification that he anticipates, involving a systematic synthetic reconstruction of natural humans “part by part, using cells.” However, although ostensibly for the purpose of repairing lost organ functions, the goals and limits of this therapeutic modality are not defined.

Whole areas of relevant science, including synthetic biology, genome writing, recoding, *in vivo* cellular engineering, hypoinmunogenic technology, and reprogramming, are largely ignored. There is, furthermore, an uncomfortable moment when, doubtless inadvertently, and incorrectly in the case of somatic interventions, Mukherjee uses phraseology with apparent eugenic overtones. In the context of gene editing designed to lower cholesterol, he asserts that this would be the ultimate feat of cellular reengineering for heart disease, as it would allow “the river of life” to be “cleansed forever.”

You Say You Want a (Cellular) Revolution

The English biologist Lewis Wolpert described cell theory as “one of the great triumphs of biology.” Its genesis, attributed to Theodor Schwann and Matthias Schleiden, is detailed by Schwann who recounted in October 1837 how “one day when I was dining with M. Schleiden, this illustrious botanist pointed out to me the important role that the nucleus plays in the development of plant cells. I at once recalled having seen a similar organ in the cells of the notochord, and in the same instant I grasped the extreme importance that my discovery would have if I succeeded in showing that this nucleus plays the same role in the cells of the notochord as does the nucleus of plants in the development of plant cells.”

Schwann’s epiphany, Mukherjee tells us, led to the realization that “a deep unity of organization and function ran through living beings.” This led the German biologist Rudolf Virchow to declare that “the body is a cell state in which every cell is a citizen.” He then transformed this insight into the science of cellular pathology, realizing that “every pathological disturbance, every therapeutic effect, finds its ultimate explanation only when it’s possible to designate the specific living cellular elements involved.”

Every cell, Mukherjee informs us, referencing the way in which each distinct cell type has an idiosyncratic pattern of gene expression, has its own “individual song.” Some cells, however, have the potential to sing many different songs. These include pluripotent stem cells, whose progeny are able, collectively, to cover the entire repertoire of songs furnished by the contemporary human genome. The different clones comprising a tumor scream out a series of inchoate, uncoordinated, and incoherent songs that deafen even the most disinterested listener.

Mukherjee says that “a cellular revolution is unfolding” and that this will transform the practice of clinical medicine. Faulty parts and missing functions can and will be rebuilt and repaired with engineered cells. In some cases, they will sing

new and artificial never-before realized songs. Songs that combine features of existing cells, and others that sample the mathematical space of possible cell types that have never previously existed.

Similar to Stockhausen's compositions, the results of such explorations in the world of synthetic cell biology may be pleasing to some. Others might find them distasteful. Mukherjee is correct in his conclusion that the limits of such endeavors must

be defined consensually by the active participation of a representative caucus of humankind. But he writes, "we have thrown open the black box of cells." It is hard not to agree with his assertion that "to snap the lid shut now might be to foreclose the possibility of a magnificent future."

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