

A New Way of Looking at Cancer

Siddhartha Mukherjee wrote the book on cancer. Can he transform the way it's treated?

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Most years, Siddhartha Mukherjee, the [Columbia oncologist](#), cancer researcher, and author, travels with his wife, the artist and fellow Columbia professor Sarah Sze, and the couple's two young daughters to the southern coast of Mexico. There the family vacations in a beach house designed and owned by Mexican artist Gabriel Orozco, a close friend. Orozco's house, a small but dazzling open-air structure inspired by the eighteenth-century Jantar Mantar astronomical observatory in New Delhi, is perched atop a rocky cliff with a panoramic view of the Pacific Ocean. "It's

an isolated place, very quiet, with no distractions,” Mukherjee says. “Great for thinking.”

A few years ago, while playing with his daughters on the house’s patio, Mukherjee had a flash of inspiration. “We were creating stencils by drawing familiar objects and then cutting out the shapes with scissors,” he says. “I made a stencil of a seabird and painted it, first making a black bird and then, by tracing the cutout, a white bird framed in black.” Staring at these yin-and-yang images, Mukherjee, who at the time was writing his 2016 book *The Gene: An Intimate History*, began to envision a pair of cells. “I saw a healthy cell and its malevolent twin — the cancer cell. And I thought to myself, ‘We’re pretty good at killing the cancer cell. We’ve got lots of drugs to do that. But why don’t we figure out a way to protect the healthy one?’”

It was a moment of epiphany for Mukherjee. A therapy that could somehow shield healthy human cells from the toxicities of cancer drugs would, he knew, revolutionize treatment for many forms of the disease. The idea was at once elementary and elegant; Mukherjee was immediately consumed by its promise.

The problem with most cancer drugs, as Mukherjee explains in his 2010 Pulitzer Prize-winning history of the disease, *The Emperor of All Maladies*, is that they are lousy at distinguishing between cancer cells and healthy cells. This is because cancer cells are genetically, metabolically, and structurally very similar to normal ones. They are, he writes, “hyperactive, survival-endowed, scrappy, fecund, inventive copies of ourselves.”

Traditional chemotherapy drugs, which still form the backbone of most cancer-treatment regimens, are designed to combat cancer cells by turning one of their most frightening and unusual characteristics — their tendency to proliferate very quickly — into a vulnerability. The drugs work by weakening the mechanisms that all cells in the body use to divide and duplicate, thus ensuring that any cells that frequently make copies of themselves eventually perish when they try to reproduce. But some healthy tissues, like those of the bone marrow, skin, guts, and hair follicles, are also constantly renewing themselves, and so cells in these parts of the body are damaged by chemotherapy too.



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Mukherjee is all too familiar with the toxic side effects of chemotherapy. Having treated blood cancers for nearly two decades, he has on countless occasions endured what is for any physician a soul-crushing experience: watching a patient suffer terribly at his own hands, as the result of treatments he has administered. This is, in fact, precisely what his job as an oncologist requires. To have any chance of saving his patients' lives, Mukherjee often must push their bodies to the brink of death, pumping them full of substances that inflict nearly as much damage on healthy tissue as on the malignancies they were intended to cure. Of chemotherapy's side effects, the weakening of the bone marrow is by far the most dangerous, since healthy marrow is needed to continually generate fresh blood. In fact, the amount of chemotherapy given to a patient is typically limited by the amount of stress the bone marrow can withstand. Unfortunately, the lower the dosage, the lower a patient's chances of being cured.

Cancer experts, frustrated by the scattershot approach and physical toll of chemotherapy, have long sought new regimens. And in the 1990s, as geneticists were mapping the human genome and decoding the specific DNA of cancers, they started to design drugs that zero in on tumors more precisely. The most effective of

these “targeted therapies” go after proteins and other molecules found only in cancer cells. However, because most cancers can be caused by many different genes, and because these genes’ molecular products are often too slippery or oddly shaped for drugs to bind to, scientists have still struggled to find good targets. Often they have resorted to creating drugs that go after molecules not entirely unique to tumors. Even some of the newest cancer treatments, such as immunotherapy, which unleashes the body’s natural defenses against cancer, may rely on this imperfect strategy, programming the body’s immune system to attack entire categories of cells — certain types of blood, skin, breast, or lung cells, say — rather than cancer cells specifically. As a result, targeted therapies can also cause life-threatening side effects such as organ failure, forcing physicians to halt the treatments early.

Playing with his daughters on the coast of Mexico that morning, though, Mukherjee saw another way. He imagined creating a new kind of therapy, one that could protect healthy cells during treatment, thereby enabling patients to take more medicine and increase their chances of survival. But how would the therapy work? How would it be delivered to the cells that needed protection? Mukherjee, whose research had until that time focused on how cancers form, had never developed a treatment before. Part of him wondered if the idea was overly ambitious. Some physicians were sure to balk at the prospect of preventing the side effects of one therapy by administering a second. And yet Mukherjee also believed that there was something satisfyingly simple about the idea of armoring healthy cells against chemotherapy. In fact, after reflecting on it for a while, he became convinced that the reason no one had proposed the strategy before was because in some respects it was *too* simple. For decades, scientists working on new cancer treatments had been striving to understand the complex biology of the cancer cell itself, hoping to find a weakness to exploit. Much less attention has been paid to the healthy cells around it. Perhaps he and his scientific peers had been looking at the situation with blinders on.

“The greatest challenge in oncology has long been thought to be identifying unique features in tumors to attack,” Mukherjee says. “But nobody has asked: why don’t we alter the healthy cell, in order to make the cancer cell a more unique and obvious target?”

Mukherjee, who is fifty, was born and raised in a middle-class area of New Delhi. The son of an automobile executive and a schoolteacher, he was a dreamy and private child, obsessed with Indian classical music and the poetry and songs of

Rabindranath Tagore. In high school, he gravitated toward Shakespeare, Flaubert, and Orwell; at the same time, he fell in love with the life sciences. “I had an incredible biology teacher who talked to us about the big unanswered questions in the field,” he says. “Like why, if all of your cells contain the same DNA, do they take on different functions? And how do they come together to form a whole organism? There seemed to be so many possibilities for discovery.”

In 1989, Mukherjee moved to the US to study biology at Stanford. He says he soon broke away from the “bio gang,” enrolling in as many philosophy, ethics, and history of science courses as would fit his schedule. The notebooks of Charles Darwin had an especially powerful impact on him; Mukherjee was struck by the naturalist’s accessible prose and the relaxed, almost playful way he presented his ideas. “I remember seeing his first sketch of an evolutionary tree and how he’d scribbled ‘I think’ above it — as in ‘Maybe I’m right, maybe I’m not,’” Mukherjee says. “I loved that. I felt totally liberated by it. Afterward, when taking science or math exams, instead of saying to myself, ‘Oh my God, I have to get this answer right,’ I began to approach problems with a sense of joy and creativity, thinking, ‘Why don’t I play with this question and see what I can do with it.’” Mukherjee was also moved by the books of Oliver Sacks and Lewis Thomas, physicians who approached their clinical work with deep curiosity and open minds. “They showed me that practicing medicine could be a process of discovery,” he says. “And I decided that’s what I wanted to do — I wanted to be a doctor who discovers things.”



Mukherjee in his Manhattan home. (Allison Michael Orenstein)

After studying immunology at Oxford University on a Rhodes scholarship, Mukherjee enrolled in Harvard Medical School, where he chose to specialize in oncology. Cancer had long been a part of his world, having claimed the lives of a young cousin, an aunt, and a high-school English teacher, and Mukherjee had a hunch that he was suited to the work. Upon entering the cancer center at Boston's Massachusetts General Hospital for the first time in 1997, as a third-year medical student attending rounds, he realized he had made the right choice. "You walk in there, and all of a sudden the world is upside down," he says. "People are having poisons dripped into their blood, some are dying, others are being saved, and every conversation you have carries a kind of potency that you just don't encounter in the rest of the world."

It is immensely challenging, both intellectually and emotionally. It was a good fit for me. I enjoy talking to people about their lives and listening. I found the whole thing exhilarating.”

Yet if treating cancer patients was an awakening for Mukherjee, it also threatened to swallow him whole. His first couple of years as a practicing physician at Mass General, he says, were in many ways the most difficult of his life. Exhausted by the rigors of round-the-clock rotations, living a lonely existence in a small apartment near Harvard Square, and witnessing death almost daily, he began to brood about the ethical dilemmas inherent in his profession. He wondered: How much chemotherapy was too much to give a person? What if a patient insists on more treatments when the effort is clearly futile? What should you tell a person whose blood tests indicate that she is cancer-free but whom you suspect has undetectable traces that might kill her? To process his thoughts, Mukherjee began to write. Every night he would fill diaries with observations, insights, and confounding questions drawn from his rounds. The next day, he would set out to find answers by speaking to senior colleagues or doing research at the library. “Writing was at first a very personal endeavor for me,” he says. “It was just my way of becoming a better doctor.”

That changed one day in 2006, when a patient asked Mukherjee a pointed question. “She was a very spirited, larger-than-life character who’d been through several courses of cancer treatment, none of which had worked, and I was offering to put her on yet another experimental medication,” he recalls. “And she said to me, ‘All right, I’m willing to go along with you. But what exactly am I doing? You have to explain this to me.’” The question demanded a thoughtful response, and while providing the woman a matter-of-fact description of her prognosis, which was poor, Mukherjee sensed the inadequacy of his reply. “I could tell that she wanted more,” he says. What precisely did she want to know? Mukherjee wasn’t sure. Maybe answers to some of the same kinds of questions he’d begun grappling with: Are experimental cancer drugs typically worth trying, or do they merely prolong patients’ suffering? Do lessons gleaned from failed drug trials at least benefit future generations? How much better have cancer treatments actually gotten over the years? In other words, what did all the pain and anguish he witnessed every day add up to? Mukherjee went online in hopes of finding a book to recommend to the patient. To his surprise, he discovered there was none that provided an accessible yet intellectually satisfying history of cancer treatments. So that night, sitting in his

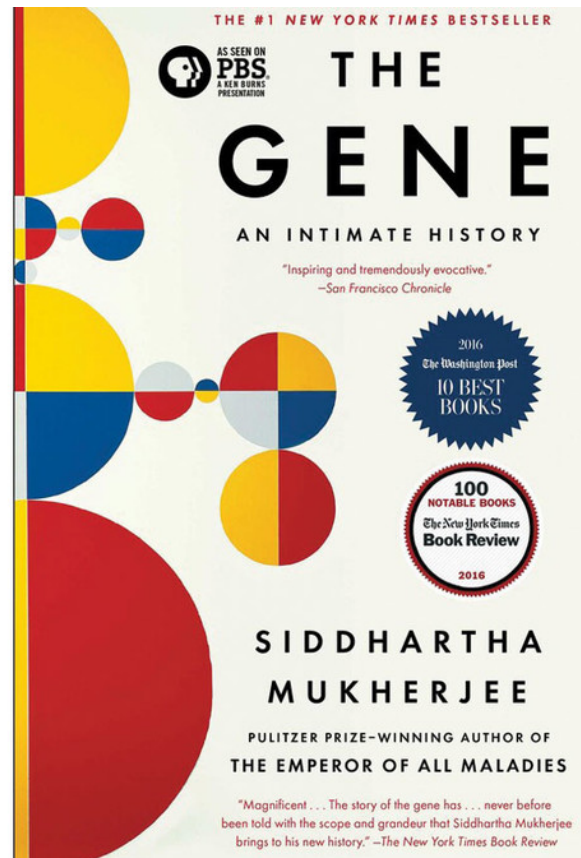
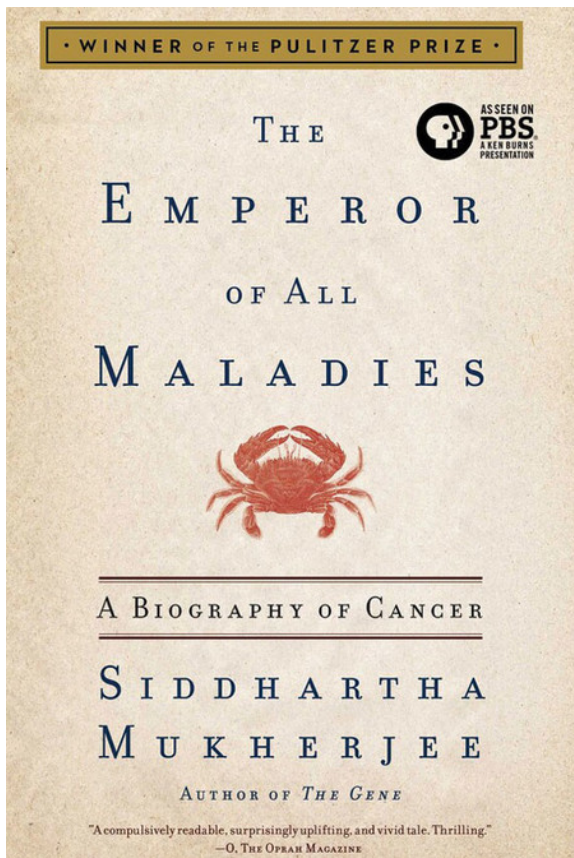
car outside the hospital with his diary on the passenger seat, he decided that he would write the book himself.

Over the next five years, Mukherjee spent nearly all his free time poring over old scientific papers and textbooks; interviewing scientists, physicians, and patients; and mining his own clinical and research experiences for clues about where the field of oncology was headed. (Mukherjee had by this time become a specialist in blood cancers and was conducting research on how bone-marrow irregularities can cause blood cells to become malignant.) He wrote most of what would become *The Emperor of All Maladies* in bed at night, next to his wife, Sarah, who read and edited his pages as he wrote them. What eventually emerged was a genre-defying masterpiece that manages to turn the entire history of oncology into a thriller, with all the major clinical setbacks and breakthroughs seen through the eyes of those who experienced them.

The book, which was published in 2010, the year after Mukherjee was recruited to Columbia, explains the biology of cancer in intricate detail and provides a generally upbeat assessment of the state of cancer medicine, emphasizing the significant progress made since the 1980s in treating certain kinds of breast, prostate, skin, testicular, thyroid, cervical, and blood cancers. It is also a riveting intellectual history, showing how theories about the disease have evolved in lockstep with scientific and technological advances. The invention of anesthesia in the nineteenth century led surgeons to insist that cancer would be cured by carving ever larger chunks out of patients' bodies; the development of antibiotics in the mid-twentieth century inspired a generation of scientists to hunt for cancer-causing pathogens; today, in the age of genomics, scientists brim with confidence about DNA research leading to a cure. "Every era," Mukherjee said in an interview at the time of the book's release, "casts cancer in its own image."

The Emperor of All Maladies, which, in addition to winning a Pulitzer Prize, was turned into a six-hour [PBS documentary](#) by filmmakers Ken Burns and Barak Goodman '86JRN, has made Mukherjee an international literary star. Cancer survivors now stop him on the street and tell him that his book helped them to understand what was happening to their bodies and enabled their loved ones to grasp what they were going through physically, emotionally, and spiritually. Other oncologists pull him aside at conferences and tell him that his book, by putting their work into a historical context, gave it more meaning.

For many, the book provided answers, but for Mukherjee the questions just kept coming. Having explored the insidiousness of the cancer cell, he soon turned his attention to the healthy cell, with an eye toward understanding how its DNA kept it functioning in perfect harmony with its neighbors. His next major work, *The Gene: An Intimate History*, traces the evolution of the concept of the gene, from the ancient Greeks' purely abstract notion that our bodies are built from instructions contained in sperm to the nineteenth-century botanist Gregor Mendel's discovery of the statistical patterns of inheritance to modern biochemists' decoding of our DNA. The book, while elucidating some of the knottiest aspects of genomic science, is also a deeply humanistic meditation on tolerance, compassion, and humility. Its central message is that although we are on the cusp of being able to reprogram nearly all aspects of our bodies, we should resist doing so in all but the rarest of circumstances (such as to treat severe illness), since genetic variety is both the key to our species' adaptability and a reminder to accept and embrace one another's differences.



Two of Mukherjee's books have been turned into PBS documentaries.

If *The Emperor of All Maladies* and *The Gene* elevated public discussion about cancer and genetic research, the experience of writing the books also invigorated Mukherjee's own laboratory work in unexpected ways. After spending years charting

the trajectories of the intertwined fields, Mukherjee emerged bursting with ideas for new scientific projects, including ones that might focus almost exclusively on healthy cells. The way he saw it, the field of oncology was poised to enter a new era as some scientists were beginning to view cancer in a more holistic manner, investigating how a wide range of metabolic, hormonal, vascular, immunological, and dietary factors can influence the disease. At the same time, Mukherjee was convinced that powerful new gene-editing technologies would soon enable him and others to manipulate the human body to make it less hospitable to cancer. He thought that these efforts could complement those of the scientists who were attempting to create drugs that target cancer-causing molecules inside tumors — a project that has dominated cancer medicine since the 1990s but which hasn't produced nearly as many breakthroughs as expected.

“The era of genomics-based cancer medicine, with its dream of identifying the mutations that cause patients' tumors and providing 'personalized' treatments, got off to an exhilarating start with the development of targeted therapies like Herceptin and Gleevec,” says Mukherjee, referring to two drugs that have essentially cured certain breast and blood cancers, respectively. “But since the 2010s, it has become clear that efforts to extend this approach to other cancers, on the whole, have been fairly disappointing.

“So my attitude is, we've got to rethink this road we've been traveling down,” he says. “I know, because I helped map it.”

On a recent Wednesday morning, in a brightly lit laboratory at Columbia University Irving Medical Center, a molecular biologist named Florence Borot gently squeezes a drop of pale pink liquid onto a glass slide.

“Now I'll look to see how many healthy cells we've got in the sample,” she says, placing the slide under a microscope.

Borot is a member of Mukherjee's research team, and the liquid is precious material: it contains blood-forming stem cells that have been extracted from a cancer patient's bone marrow. “We're going to genetically engineer them to be invisible to cancer drugs,” she says.

Her project is one of a half dozen in Mukherjee's lab that aims to fight cancer by manipulating healthy tissues. Most of these projects are focused on improving treatments for an unusually aggressive form of blood cancer called acute myeloid

leukemia, or AML. One of the deadliest cancers, AML kills approximately two-thirds of all people who are diagnosed when they're under the age of sixty and 90 percent of those diagnosed when they're sixty and over. It occurs when immature blood cells grow out of control, eventually taking over the bone marrow and pouring into the bloodstream. "It's an incredibly virulent and explosive form of cancer that can kill quickly, often within months or even weeks," says Mukherjee, who has seen hundreds of patients with AML.

Acute myeloid leukemia also illustrates the limitations of genomics-based cancer therapies. Despite dozens of papers on AML's genetics having been published over the past quarter century, little progress has been made in treating it. "We know its biology and genetics inside out," Mukherjee says. "Yet none of this research has suggested any effective therapies. For the most part, we're still treating AML with chemotherapies developed in the 1960s and '70s."

The pharmaceutical giant Wyeth (now part of Pfizer) did create one targeted therapy for AML in the 1990s. Called Mylotarg, the drug targets a protein that does not cause cancer but is located on the outer surfaces of blood cells of the type that AML afflicts. (These "myeloid" cells include several varieties of the white blood cells that serve as the body's first line of defense against viruses, bacteria, and other invaders.) Mylotarg, whenever it comes across a myeloid cell, will grab on to its surface protein and then inject the cell with a toxin that tears it apart. The drug is frighteningly efficient at killing myeloid cells; unfortunately, in the course of destroying cancerous myeloid cells, it also wipes out patients' remaining healthy ones. This can cause their immune systems to crash, making them susceptible to life-threatening infections before their cancer is defeated, among other side effects. As a result, the drug has an unimpressive track record; one study a few years ago found that it harmed more patients than it saved and was, in some circumstances, even more dangerous than traditional chemotherapy.

"It's not an ideal drug," says Mukherjee.

But he thinks he can make it a better one. How? By stripping patients' healthy blood cells of their telltale surface protein. (The protein in question is an antigen, a type of molecule that serves as a cell's identification card, announcing its presence to other cells in the body but fulfilling few operational functions.)

A couple of years ago, Mukherjee and several of his CUIMC collaborators — including professor of medicine [Azra Raza](#), research scientist Abdullah Mahmood Ali, and Florence Borot — achieved a milestone. In a series of experiments reported in the *Proceedings of the National Academy of Sciences*, they managed to completely eliminate AML from sick mice by simultaneously giving the animals Mylotarg and infusions of stem cells that they had genetically altered to produce myeloid cells that are invisible to Mylotarg.

“Since the drug only attacked leukemic myeloid cells, the mice were able to tolerate it for longer than they otherwise would have been able to,” says Borot, who used the gene-editing technology CRISPR to make the alterations to the stem cells. “This gave the medicine more time to do its job.”



Mukherjee in his CUIMC lab with Florence Borot and Abdullah Mahmood Ali. (Eileen Barroso)

The experiments, which followed years of laboratory preparations, sent ripples of excitement through the biotechnology and pharmaceutical communities, and Mukherjee helped launch a startup, Vor Biopharma, with the goal of one day bringing his team’s therapy to hospitals and clinics. The Boston-based company is planning to soon initiate a clinical trial that will give Mylotarg in tandem with Vor’s therapy to AML patients who have failed to respond to traditional chemotherapy.

(Chemotherapy remains the standard treatment for the disease because Mylotarg has performed so poorly.)

Mukherjee, who serves as a scientific adviser to Vor Biopharma, believes that his team's therapeutic strategy could be adopted to improve the potential of other leukemia drugs, many of which work similarly to Mylotarg in that they go after surface proteins found on both cancerous blood cells and some healthy cells.

Still, it is an open question whether Mukherjee's new therapy will prove safe and effective. Experimental cancer treatments frequently succeed in mice only to fail in human trials. And this therapy, because it would permanently alter the DNA of a person's blood-forming stem cells and hence their blood, comes with deep uncertainties. Scientists have barely begun to understand how the approximately twenty thousand genes in each of our cells interact with one another, and edits made in one part of the human genome have often been found to trigger unintended consequences. So it is difficult to predict exactly what will happen when millions of the Columbia team's genetically edited blood cells are infused into a patient's body. Will the cells fail to work properly, perhaps because the surface protein performs important functions that scientists aren't yet aware of? Or will the cells work well initially but cause unanticipated health problems years down the road?

There is reason to believe that the surface protein being removed from blood cells is not physiologically essential. To minimize the risk of complications, though, the researchers are now finessing their gene-editing technique. Rather than removing the protein entirely, they plan to alter its shape so that Mylotarg cannot attach to it.

"If the protein has a biological function that we're not aware of, then hopefully it will still be able to perform it," says Borot, who is leading the gene-editing effort.

For Mukherjee, the human trials cannot come soon enough. In the twenty years he has cared for people with AML, he estimates, he has lost about one patient per week. Other oncologists now telephone him regularly, asking when the trials will begin.

"It's true that there are many things that could go wrong," he says. "The whole project is operating on a knife's edge. But it's also possible we'll save many people's lives."

It is midmorning on a Tuesday, and Mukherjee is leaning back in a swivel chair in his book-lined office on Columbia's medical campus. He has just pulled an all-nighter to finish writing a grant application. He has dark circles beneath his eyes and his floral-print shirt is ruffled, but he is warm and engaging, and he grins while indulging a question that he has obviously heard many times before.

"People often ask me whether I'm a writer, a scientist, or a doctor first," he says. "And I always say that I can't distinguish between these roles. What I do as a historian and journalist and my work as a scientist and physician are all integrated for me. History is alive with ideas that we can use to inform treatments today, if we pay close enough attention."

A case in point: Mukherjee says that the writings of the Victorian English surgeon Stephen Paget are a constant source of inspiration to him in the laboratory. In 1889, Paget, after observing that some organs are likelier than others to host cancerous tumors, hypothesized that surrounding tissues play powerful and mysterious roles in nurturing the disease. His theory, which holds that cancer cells are "seeds" dependent on finding fertile "soils" to grow in, was ignored for more than a century but has in recent years been embraced by scientists.

"Paget is somebody I'm in conversation with regularly," says Mukherjee, noting that the physician's writings were on his mind when he came up with his novel idea for treating AML. "I try to view cancer through his eyes. He had a powerful and fresh vision."

Inspired by Paget, Mukherjee and his team are currently investigating the ways cancer cells evade the body's immune system. They recently discovered part of the answer, finding that cancer cells hide among certain kinds of healthy blood cells, possibly by mimicking their intracellular chemical signals. "The next step will be devising ways to clear those healthy cells away from tumors, so that the immune system is able to recognize the cancer and attack it," Mukherjee says.

In addition, he is examining how our eating habits may influence cancer and its treatment; this work follows up on a groundbreaking study that he and Cornell cell biologist Lewis C. Cantley published in 2018, which showed that a high-fat, low-carbohydrate diet improves the effectiveness of a cancer drug called Aliqopa in mice. Other researchers at Columbia's and Cornell's teaching hospitals are now overseeing clinical trials to determine if the diet has the same benefit for people

with lymphomas and endometrial cancers.

“The effects of diet on cancer have long been neglected by oncologists because it was seen as kind of a loosey-goosey area — a lower science and the domain of unregulated ‘nutraceutical’ companies,” Mukherjee says. “So the research is still in its early stages. It’s not like I can tell you, ‘Eating blueberries will prevent cancer,’ or anything like that. But we’re beginning to conduct fine-tuned metabolic studies to see how the environment in which a cancer grows, and in which a drug combats it, might be shaped by what you eat.”

Mukherjee still sees patients at CUIMC one day a week and writes every morning, often exploring the ethical challenges that physician-scientists confront in their work. It is a rich subject, ripe with cautionary tales from oncology’s past. Indeed, *The Emperor of All Maladies* is brimming with stories of physicians who, in their quest to save cancer patients, cause them pain and anguish. The mid-twentieth-century surgeons who, in a misguided attempt to prevent breast cancer from spreading, carved out large sections of women’s chests and shoulders. The pediatric oncologists who in the 1980s pumped as many as eight chemotherapy drugs at once into children’s spines in failed attempts to treat their brain tumors. And the physicians who, in that same decade, launched an ill-advised bid to shrink solid tumors in adults by giving them enormous quantities of chemotherapy drugs that had only ever worked on blood cancers. These treatments disfigured, sickened, and in some cases killed cancer patients who might otherwise have enjoyed a measure of peace in their final days. Shoddy research sometimes played a role, as did, Mukherjee suspects, scientists’ professional ambitions. But more often than not, he believes, it was physicians’ desperation to save lives that led them to underestimate the risks they were taking. Mukherjee meditates on these and other dark chapters from his field’s history in hopes of avoiding the same mistakes.

And yet the difference between a triumphant and a disastrous human trial is often only apparent in hindsight. Major advances in cancer care, Mukherjee says, almost always involve “inspired leaps of faith” on the part of clinicians and patients, since no amount of laboratory research can ever predict exactly what will happen when an experimental therapy is introduced to the human body. He points out that one of the first forays into immunotherapy nearly ended in calamity when, in 2010, the immune cells of a five-year-old leukemia patient named Emily Whitehead were genetically altered to make them attack her cancer. Whitehead’s immune cells got confused and attacked the rest of her body, too, almost killing her; doctors managed to

stabilize her only because one of them had a young daughter with a rare autoimmune disorder and therefore happened to know of a drug that would quell her immune response. In the end, Whitehead beat her cancer, and the episode, which could easily have provoked a regulatory crackdown on immunotherapy, energized the field and provided a template for managing the new therapies' side effects.

“There is still an element of art in medicine,” Mukherjee says. “If you push too hard, you’re risking your patients’ lives. But if you don’t push hard enough, you’re not doing all that you can to save them. Knowing where to draw that line is very difficult.”

There was a time, Mukherjee remembers, when he loved just one thing. From the age of seven into his teens, his life revolved around singing ragas, the classical music of India. He was a prodigy, receiving lessons daily from some of New Delhi’s most prestigious vocal instructors and being groomed for a career as a concert performer. He recalls how the music brought him peace, how his voice merged with the mellifluous sound of the sitar and then soared effortlessly above it — “like a bird.”

Mukherjee continued to sing seriously for many years, then, during his junior year at Stanford, he decided rather abruptly to give it up. Part of him doubted that he had the raw talent necessary to go professional. But there was something else, some intangible quality that he thought his singing lacked, a certain gravitas and emotional depth that he could hear in the performances of his favorite singers, like Amir Khan and Shahid Parvez.

“I just didn’t have the grief you need,” Mukherjee says. “I’d lived a relatively charmed life up until that point. I hadn’t really experienced much loss. I hadn’t treated cancer patients. So I was just singing in an athletic way, like it was a sport. There was nothing behind it.”

Now decades later, Mukherjee has begun to sing again. He has put together a group of New York City-based musicians that, prior to the COVID-19 pandemic, performed at small clubs and museums, mixing traditional Indian music, jazz, and blues. “I’ve been experimenting with creating a more colloquial, conversational singing style that draws on twentieth-century Western musical traditions,” he says. “One of the things I always admired about Indian classical singing is that authenticity of voice is supremely important, even more so than technical skill. You have to sound like

yourself. So I've been searching for a deeper way to be myself now in my music."



Mukherjee, a classically trained singer, says his experiences in the arts have helped him find his "voice" as a scientist. (Allison Michael Orenstein)

Mukherjee is currently working on three books: a history of cell biology, which he sees as a prequel to *The Emperor of All Maladies* and *The Gene* ("It's about how the conception of the human body as a conglomeration of individualized units that cooperate and sometimes compete with each other changed medicine"); a collection of new and previously published essays about how damaged biological systems can restore themselves; and an updated edition of *The Emperor of All Maladies*, which will contain new sections on immunotherapy and the rising costs of cancer medicines. In the past year, he's also managed to write a series of *New Yorker* articles about COVID-19, exploring everything from the mysteries of how the virus behaves within patients to the need for America's "market-driven, efficiency-obsessed" medical system to invest more resources in preparing for unexpected crises.

When asked how he finds the time to write, his answer is pretty straightforward.

"I believe that work-life balance is overrated," he says. "And I have none — zero."

It's a way of life he shares with his wife, Sarah Sze, a prominent artist known for her [large, intricate, and arresting sculptural installations](#). Sze and Mukherjee both keep irregular hours and travel constantly, she to exhibit her artwork and he to attend conferences. They carve out time each week to focus exclusively on their daughters, who are fifteen and eleven (museum trips and movie nights are always popular). But both parents work many evenings and weekends, Sze at her studio a few blocks from the family's loft in Chelsea and Mukherjee at his CUIMC lab.

"We invite the girls to come along and even get involved sometimes, to be a part of it and enjoy it with us," says Mukherjee. "We try to show them that it's cool to be really passionate about your work — that it's something we can all be proud of as a family."

Despite all that he's accomplished, Mukherjee says that he is troubled by the compromises he must make in balancing his roles as author, physician, and research scientist. In academia, after all, scientists are celebrated for establishing themselves as experts on niche subjects, producing tons of papers, and overseeing large research staffs; Mukherjee, who doesn't claim to be an authority on any particular aspect of cancer biology, publishes more sporadically than do most scientists of his stature and runs a small lab consisting of just a handful of researchers. What energy he does have for laboratory work he pours into a modest number of high-risk, high-reward projects that aim to turn the latest breakthroughs in cancer biology into new therapies. These endeavors often involve collaborations with larger laboratories whose leaders team up with Mukherjee to help him bring to life ideas that they have hashed out together during coffee-fueled late-night phone calls. It's a strategy that Mukherjee says neutralizes his main liability as a scientist (a disinterest in immersing himself in hyper-specialized basic research) while amplifying his strengths (a freewheeling curiosity and broad knowledge of research trends). But like any polymath, Mukherjee can't help but wonder sometimes whether he would feel more fulfilled if he weren't running in so many different directions. "This multifaceted, kaleidoscopic life that I lead requires difficult tradeoffs," he says. "At a certain point, you just have to accept that you're never going to be the scientist you want to be. Or the doctor. Or the writer."

Of course, academic scientists have not always been expected to manage sprawling research operations or to spend their careers drilling deeper and deeper into narrow subfields. Before the late twentieth century, when rapid technological advances led to an explosion of knowledge and the birth of complex new questions that required

larger and costlier research enterprises, scientists were likelier to work alone or as part of small groups on less arcane subjects. Science has progressed, but perhaps something has been lost. Researchers in the past had more time to reflect on the theoretical and philosophical underpinnings of their work, to mine neighboring fields for inspiration, and to pursue more idiosyncratic visions.

In fact, the history of cancer research, as told by Mukherjee in *The Emperor of All Maladies*, is filled with dreamers, mavericks, and iconoclasts who, by virtue of having one foot outside the field of oncology, are able to look at cancer in new ways. There is the pathologist Sidney Farber, who, after years spent dissecting, measuring, and weighing cadavers in the basement of a Boston hospital, intuitively that the first attempts to develop chemotherapies ought to target leukemias, for the simple reason that leukemia cells circulate in the bloodstream and can be precisely counted before and after administering drugs. There is the biologist Howard Skipper, whose purely mathematical take on cancer inspires him to propose the novel idea that multi-drug cocktails could prevent cancer cells from evolving resistance. And there is the obstetrician and oncologist Min Chiu Li, whose obsession with analyzing patients' hormone levels convinces him that many people who are declared free of cancer actually need more treatment, leading him to pioneer "maintenance" chemotherapy regimens. These scientists, whose ideas were all controversial in their day, permanently altered the course of cancer medicine and saved millions of lives. Mukherjee the author chronicles their professional setbacks and humiliations along with their triumphs with unusual sensitivity. It's a respect he also pays to the many laboratory scientists whose painstaking investigations into cancer's basic biology laid the groundwork for clinical breakthroughs.

"One of the things you learn from studying the history of science is that there are so many different ways of investigating the natural world," Mukherjee says. "Scientists, like artists, have their own styles of working, their own voices, too." And he has come to realize that by immersing himself in philosophy, music, poetry, and fine arts, he has expanded his worldview in ways that may make him a more versatile cancer researcher. "Somewhere along the way, I thought, OK, well, maybe I'm not going to be a conventional scientist. But I can still leverage my ability to synthesize knowledge and to draw inspiration from lots of different domains to come up with new ideas for medicines. And that will be my contribution. That will be my way of helping to emancipate human beings from all of this suffering and disease. That will be my authentic voice."

This article appears in the Spring/Summer 2021 print edition of Columbia Magazine with the title "The Education of Siddhartha Mukherjee."

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