CURALINK

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thecurafoundation.org

Welcome to CuraLink—a newsletter for innovators building a healthier future for all.

Dear Cura Community,

Robin L. Smith, MD
Founder, President and Chairman, Cura Foundation

Welcome back to CuraLink, a newsletter and interview series featuring the most pressing issues in human health, unmet medical needs and the emerging innovations and technologies directed to address them.

Last month, we explored the transformational work of Dr. Angela Diaz, director of the Mount Sinai Adolescent Health Center. In New York City, Dr. Diaz and her team offer integrated physical, mental and social services to optimize the well-being of approximately 12,000 adolescents every year—at no cost to patients. This conversation is for anyone who has a teen in their life or who may be concerned with the escalating youth mental health crisis.

This November, we were honored to discuss the emerging universe of cellular medicine with Dr. Siddhartha Mukherjee. As one of the leading voices translating complex science to the public, Dr. Mukherjee has fundamentally changed the way we think about cancer in *The Emperor of All Maladies*, medicine in *The Laws of Medicine* and genetics in *The Gene*. This month, Dr. Mukherjee published the third book in what he calls the life quartet: *The Song of the Cell: An Exploration of Medicine and the New Human*.

The book offers an enlightening compilation of cellular biology, history and personal narrative told in Dr. Mukherjee's deeply personal and informative prose. *The Song of the Cell* is a joy to read, and we hope you will pick up a copy here.

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A conversation with Dr. Siddhartha Mukherjee

Dr. Siddhartha Mukherjee's days are a flurry of activity split among running his blood cancer lab, treating patients, building four biotech companies, writing books and science feature stories for *The New Yorker* and spending time with family and friends. Rare moments of stillness come when he's gazing through the lens of a microscope examining the blood smears of his patients. These samples tell the cell-based story of a patient's illness before he meets them in person.

"I've spent a lifetime with cells," Dr. Mukherjee, a hematologist and oncologist, writes. It's only natural that he would translate this lifelong cellular fascination into the subject of his latest book, *The Song of the Cell*. For decades, DNA has been biology's reigning icon. According to Dr. Mukherjee, the cell is the real unit of life and understanding cells—and their interconnectedness—has unlocked a revolution in cellular medicine.

In this month's CuraLink, Dr. Mukherjee shares the "spine-tingling" awe of bringing research to life through medicine, how to combat an "anti-science" society and how understanding the cell is key to understanding life itself.

Siddhartha Mukherjee, MD, DPhil, Author and Associate Professor of Medicine, Division of Hematology/Oncology, NewYork-Presbyterian/ Columbia University Irving Medical Center

What initially spurred your interest in medicine and why did you specialize in oncology?

My interest in medicine grew in reverse. I first completed my PhD in immunology at Oxford University studying human viruses like the Epstein Barr Virus. Then I became increasingly interested in how human beings interact with this virus. For me, research comes alive when it begins to involve medicine. My interest in health care came out of an interest in understanding the human body more deeply.

Oncology is a very emotional form of medicine. The relationship with your oncologist is one you don't have with any other kind of doctor. There is an atomic bond between a patient and their oncologist—both are dealing with a moment in life where every decision has a consequence. Every conversation, every word and every moment matters. To be so intimately involved in a person's life and their decision-making was the most exciting to me compared to other specialties.

"Cancer is the biggest medical mystery of our time, and I wanted to try to solve it."

You are one of the world's leading voices communicating science to the public. What do you hope readers take away from your writing?

When I began to write, I thought I would write differently from other science writers. I wanted to write what was personal to me whether it was a lab experiment, my own physical ailments or my family history. I write science in the most human way that I can. It's almost science as a biography. I think that's what makes my writing accessible.

One goal is to communicate the idea that science is not a linear process—there is a network effect. The second is to show that science is a human process—that people make errors.

John Maynard Keynes once said: "When facts change, I change my mind. What do you do?" Through my science writing, I hope to communicate the idea that science is a dynamic process. Facts change, but also facts remain.

We are living in a society that is very anti-science. I want to change that. I want to show people the enormous benefits that medicine has brought already and will bring and remove this false idea of the scientist as some kind of machinator. Scientists and doctors are strivers trying to make the world better for us.

After exploring fundamental laws of medicine, cancer and genetics in your previous books, what inspired you to write The Song of the Cell?

From the 1950s onwards, DNA has been the iconography of biology and life. DNA is iconic because it's one

molecule and it's beautiful. In *The Gene*, I wrote that when you look at DNA, you know it is carrying code. DNA is universal. It is in every cell in every organism aside from some viruses. What some people don't realize is that DNA is lifeless. It's the cell that brings it to life.

There is a quiet, but very provocative, claim in *The Song of the Cell* that, in fact, the real unit of life is not genes or DNA: It is the cell. The cell enlivens DNA and makes life possible. Therefore, if we want to understand life and disease, we need to think about the cell.

In some ways, the cell is the new icon because we are finally beginning to understand the song of the cell—the interconnections among cells, what they do and how they function. It's the cell that should be the center of medicine. Because it's the cell that carries out the functions of the body.

The reason cells don't occupy the same iconography as DNA is because cells are extraordinarily diverse. A neuron doesn't look like a kidney cell or a white blood cell. When I ask someone to draw DNA, they can draw a molecule of DNA. When I ask someone to draw a cell, they'll say: "Which cell?" They look so different from each other because cells are so functionally different. But in order to understand life, we need to understand the cell.

"The cell sits at the nexus of both wellness and illness."

No matter how much headway we make in our understanding of genetics, which is progressing rapidly, we will still need to understand cell biology to understand anything that happens to us—how we are made, how we function and how we malfunction.

The second provocative concept in the book is this idea of the new human. Now, having understood some cells, we're changing their cellular properties and creating humans with functionally, chemically and genetically altered cells, which we had not done even 50 or 100 years ago. Our understanding of cell biology has really changed the fundamentals of how we think about ourselves.

You talk about the "spine-tingling awe" of scientific discovery. What moments in your own life have inspired that level of awe? Why do you consider discovering and elucidating cell biology some of science's most crucial achievements?

The first time you open up a brain and realize that consciousness, sentience and sensation are somehow located in this complex tangle of neurons—that's an awe-inspiring thought. How could it possibly be that this tangle of neurons manages to produce these properties? And yet we know it does.

Similarly, the first time my mentor at Oxford and others discovered how T cells detect viruses was completely mind-boggling. A virus lodged within the cell makes proteins. Those proteins are chopped up. Little molecules pick up those viral proteins, and as if they're mounting tasting platters, they bring them to the surface of the cell where a T cell can sniff to figure out whether it's a virus or part of the normal proteins in the cell. It is spine tingling to think about the amazing evolutionary journey to go from the T cell to its capacity to sense foreign invaders in the body.

In your lifetime, you generate about one heartbeat every second. If those heartbeats go wrong, blood will stop flowing and your body will collapse. Yet, the heart does this second after second, day after day, year after year. The discovery that this muscle has a molecular machine with the capacity to contract and relax and contract and relax. That is one of the most beautiful and incredible discoveries of humanity.

I feel that the discovery of cell biology and cell function (e.g., metabolism, waste disposal and homeostasis) easily ranks as one of the greatest scientific discoveries ever made.

You describe the intricate coordination among cells, and how, when they rebel independently, cancer and illness may result; that disease is a "violation of the social compacts between cells." Why is understanding cellular dynamics essential to understanding human health and disease?

Most of all because cellular dynamics make up a social compact that keeps us alive. To understand illness, we have to understand the pathology of the cell.

The immune system is functionally created to defend ourselves from pathogens. If it were to collapse, you would be constantly invaded by pathogens. The kidneys are created to maintain salt and water balance. If those were to collapse, you become overloaded with salt and puff up. Red blood cells are meant to deliver oxygen. If those don't work optimally, then no cell in your body can function.

With COVID-19, there has been a humbling in cell biology and immunology because we thought we knew so much about viruses and how they interact with the immune system.

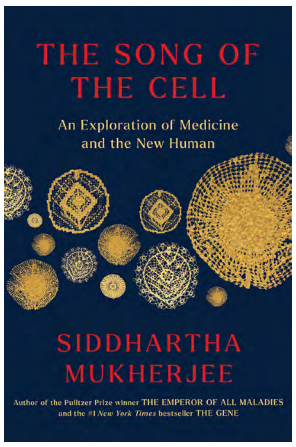
One important lesson is to what extent do we fully understand what happens when a virus infects us and begins to unleash a cascade of responses? SARS-CoV-2 is very bizarre. It causes a previously unknown form of immune dysfunction that the scientist Dr. Akiko Iwasaki has called "immunological misfiring." We didn't know any of this before. Who knew that the immune system could misfire this way?

To understand the interconnectedness among cells is incredibly important because it's this interconnectedness that ultimately leads to a functioning human body. Each system works on its own, but also communicates with other systems. The nervous system talks with the immune system; the immune system talks to all the organs in your body. To understand human beings, we need to understand ourselves as a parliament of cells.

What can The Song of the Cell teach us about ourselves as human beings and life itself? Societally, what might human beings learn from cells' cooperative behavior?

What's astonishing is, when our bodies work well, our cells respect diversity and are functionally dependent on it. We ourselves are diverse assemblages. We depend on this diversity to stay functionally stable and alive.

I hope that we learn that cooperation, diversity and functional specialization are part and parcel of how humans function. Hopefully that's true for how societies and the world function as well. Organisms can only exist with each other if they cooperate.



The Song of the Cell is Dr. Mukherjee's third book in what he calls his life quartet

You have written that cancer metastasis is not only driven by cancer cells but by their relationship to the host—or the relationship between the "seed" and "soil." Why is it important to refocus our understanding of diseases through the lens of ecological interconnectedness?

This idea emerged from an article I wrote in *The New Yorker*. Cancer is a genetic disease—mutations in genes cause cancer. And we've now sequenced hundreds of thousands of cancers. That sequencing has been helpful, but it hasn't helped us fully appreciate or understand the ecology of cancer.

That's where this book begins. We don't understand how cancer cells interact with their local environments. We don't fully understand the metabolism of cancer. We're slowly understanding the immune interactions with cancer. How does a cancer cell create a home for itself in the liver? How does it attract other cells? Why does the liver not say: "Well, you don't belong here"? It's because the cancer cells secrete factors to summon other cells to create this home for themselves.

Understanding this ecosystem is going to be crucial to understanding cancer cells and how they metastasize. I go back to this idea of seed and soil. We've focused so much on the cancer cell, which is the seed, but we also need to focus on the soil—the environment containing the cancer cell.

It goes back to a question that the great English surgeon Sir Stephen Paget posed. The liver and the spleen are almost the same size as neighboring organs. They have almost the same flux of blood through them. Yet the liver is a frequent site of metastasis for cancer, and the spleen is very rarely a site of metastases. Why? The cancer is the same. What is it about the cells of the spleen that allow the liver to be a frequent side of metastases, but not the spleen? If we found that interaction, we would find a new cosmos of anti-cancer drugs, which has been a goal for cancer medicine for so long.

The book features powerful patient stories like those of Emily and Sam who are on the front lines of cellular medicine. What have these patients taught you about the risks and benefits of cell-based medicine?

Emily's and Sam's stories are opposite. Emily Whitehead's story is a story of an incredible success. This young woman had leukemia and was treated with cellular therapy. Her T cells were extracted, weaponized and re-infused into her body to achieve remission.

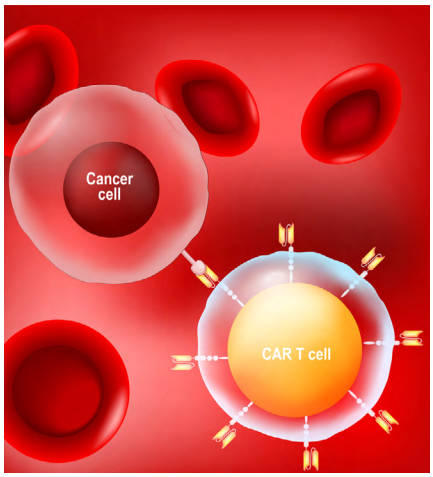
My friend Sam received a different immunotherapy. He was given a drug so that his cancer cells became visible to the immune system. But, unfortunately, that drug also caused an autoimmune reaction and eventually

stopped working. What was astonishing about Sam's case is that his tumors were almost geographically dependent on these therapies. In some sites of his body, they would respond to the immunological therapy, and in some sites, they wouldn't. Why? What is special about your ear versus your liver? We don't know.

So these two counterposed stories, both having to do with changing the functional biology of cells in the immune system, ultimately remind us that while we have done so much, there's still so much left to learn in cell biology.

A company that I started is doing the first Phase 2B trial of CAR T therapies in India, where CAR T was previously inaccessible. Getting that study off the ground created an incredible sense of hope, but also a sense of wonder. We had people working through the pandemic to create this cellular factory that allows us to grow T cells, weaponize them and put them back into a patient's body. It's exhilarating.

One of the most gratifying moments of my life was to see that first child with relapsed leukemia go into remission after CAR T therapy. It's very difficult to convey to someone who doesn't work in medicine the joy of seeing that work translated into saving a human life.



A visualization of Chimeric antigen receptor (CAR) T-cell immunotherapy. Dr. Mukherjee's company Immuneel is currently testing CAR T-cell therapy in India, making previously inaccessible therapeutic options available to underserved cancer patients across the country

In the book, we learn about innovations like deep brain stimulation, immunotherapy, IVF and stem cell therapy. What is the significance of these developments, and what have been the most impactful breakthroughs in cell-based medicine of the past two decades?

Understanding cellular physiology has enabled many medicines; so it would be hard to choose one or the other. I work in immunology and cancer. So obviously, CAR T-cell therapy—T cells that are weaponized to kill cancer cells—has been an enormous development and resulted in curing children with relapsed leukemia, which was otherwise incurable.

Immunotherapy, which we would not understand if we had not understood cell function, surveillance and how cells can be made to kill cancer cells, has also been an enormous discovery. Bone marrow transplantation and blood transfusions are cellular therapies. IVF, which has led to the birth of hundreds of thousands of babies worldwide, is a cellular therapy.

"We are in the middle of a cellular therapy revolution."

Part of that revolution has happened and part of it is yet to be. And so this is a time to step back and understand how these revelations came about. We have to simultaneously consider the cell as an autonomous, atomistic and single unit of life, as well as a holistic, functional unit that must cooperate with other cells to create and sustain life.

What are the cellular therapies currently emerging that you are most excited about? What are the therapies, perhaps similar to IVF, that were seen as very radical that may move from the fringe to mainstream?

One idea I'm excited about is precision nutrition. My colleague, Dr. Lew Cantley, and I recently found that manipulating the human body metabolically, in combination with drugs, could help treat cancer. These findings were published in *Nature*. We founded a precision nutrition company called Faeth, which works on developing this.

Another arena that I have worked a lot on is harnessing our knowledge of genetics, including CRISPR and cell biology, to create a radically new way to treat acute myeloid leukemia, a disease that has a very dismal prognosis. We created another company based on this work called Vor Bio, which is conducting clinical trials.

I love researching some of the most basic scientific questions. But the real thrill for me is when something becomes a cell-based medicine. In the future, our deepening understanding of how cells communicate with each other, how metastasis is set up, how the immune system surveys that metastasis and why a cancer cell doesn't get rejected—these are the real frontiers.

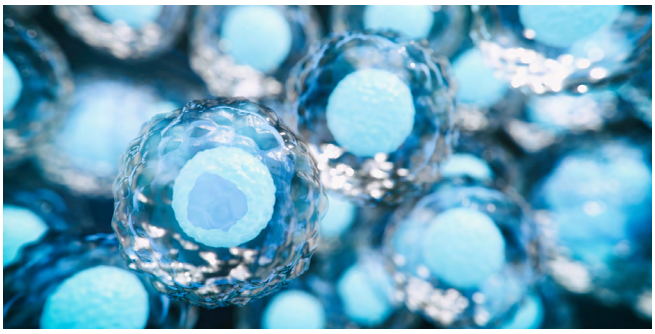
What should people understand about the risks and benefits of tampering with cellular properties via cellular engineering?

The major thing to understand is that if you're taking cells from someone else's body and putting them into yours, there's a major risk that your immune system will reject them. We need to find a way to suppress your immune system, so that the foreign cells aren't rejected. That carries risks because you're exposing yourself to potential infections and other diseases. We see these risks often in bone marrow transplants.

The moral here is that cell therapies, including stem cell therapies, are extraordinarily powerful because they change the basic unit of life. But it comes at a price. When you tamper with the basic unit of life, you need to figure out how it is interacting with the body as a whole.

You can't just chuck a cell into a body, which you might be able to do with some drugs. Once the cell is inside the body, it becomes part of what I call the new human and has to interact with other systems in the body, including the immune system. Once it starts that interaction, we need to ensure that it doesn't turn dangerous or violent or turn on itself.

What should the public understand about the therapeutic power and complexity of stem cell therapy and how it may transform the way we treat various diseases including cancer?



Stem cell therapy shows extraordinary therapeutic potential but Dr. Mukherjee cautions, "It's not magic"

There are a lot of misconceptions about stem cell therapy that the Cura Foundation has been very helpful in clarifying. First of all, stem cells are often misclassified. We need to be very careful about understanding which organs repair and rejuvenate themselves through stem cells and which organs don't. The public often uses the word stem cell as if it's one thing but different organs have different repositories of stem cells. And only certain ones can be regenerated and renewed. Those cells are the likely targets of medicines and medical therapies.

The public needs to understand that when you use the word stem cell, it's not magic. But in fact, we need to ask: Is it really a stem cell? Can it self-renew? Does it have a therapeutic role? Can it be grown?

One big challenge in stem cell therapy is that when stem cells degenerate and die, you cannot bring them back. Stem cell therapies are extraordinarily promising because of the potency of the cell. But you have to catch the cell while it's still alive or transplant it so that you can mobilize its potential. So it's unlike some other diseases, where you're treating a cell that already exists in the body.

Thousands of clinics around the world, in places with looser regulations, offer stem cells to cure X disease, whatever it might be. You have to be really thoughtful about determining the type of stem cells, the risks and their origin. What's the proof that this form of cellular therapy is going to work? The United States has been very thoughtful about this. Cellular therapy goes through a very rigorous evaluation process.

My general plea is: Don't be hypnotized by the term stem cell. Cellular therapy is an astonishing thing, but it has a long way to go. Follow the scientific literature.

Is there a central inquiry in cellular medicine and biology that, if answered, would blow open the field or perhaps a question that keeps you up at night? What does the future hold for cellular medicine?

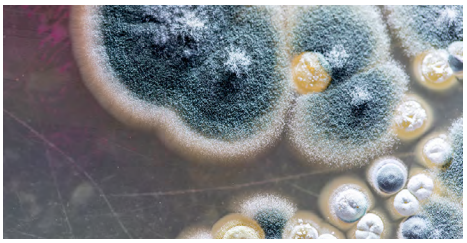
I don't think there's a single central question, but a family of questions: How do cells communicate with each other? How does their nutrition and metabolism affect each other? How can we fit this jigsaw puzzle together to better understand human physiology and, ultimately, the cellular ecology of humans in a novel way?

I am excited to launch a new investigation into a microscopic world that seemed impenetrable. I want to convey the sheer excitement of how consequential this investigation is and could be down the line.

We're already doing bone marrow transplants, transplants for patients with various blood diseases and CAR T-cell transplants for patients with cancer. We're deepening our understanding of the biology, metabolism and nutrition of cells. We are in the future now.

This interview has been edited for length and clarity.

Insights, Perspectives & Ideas



Deadly Fungi Are Infecting More Americans

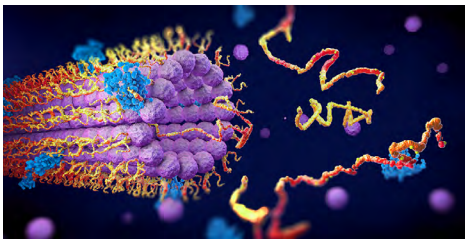
Wall Street Journal, October 2022

Fungal infections already kill more than 1.6 million people yearly, Dominique Mosbergen reports, and the toll is climbing. According to the Centers for Disease Control and Prevention and the World Health Organization, fungal infections are rising due to higher temperatures, antibiotic overuse and increased use of immunocompromising medical treatments. Drug developers and scientists are racing to develop therapies to help manage the uptick in fungal disease. Based on the escalating threat, the WHO recently created a list of fungi that it said pose a growing risk to human health, including yeasts and molds commonly found in nature and the body.

How Marion Nestle Changed the Way We Talk About Food

GQ, October 2022

Dr. Marion Nestle, one of the world's leading voices on nutrition and the Paulette Goddard Professor of Nutrition, Food Studies, and Public Health, Emerita, at New York University, has spent the past 40 years studying the evolution of the American food system. In this *GQ* interview with Sami Reiss, Dr. Nestle shares insights from her recently published memoir *Slow Cooked*. She shares how to trust common sense for what's good for you, her late-in-life fight for a healthier world and the complicated world of food politics.



One of the Biggest Problems in Biology Has Finally Been Solved

Scientific American, October 2022

Earlier this year, the AlphaFold artificial intelligence program predicted the 3D structure of every known protein—about 200 million total—rendering a previously laborious process relatively seamless. The program opens the door for applications that range from expanding our understanding of basic molecular biology to accelerating drug development. Google DeepMind CEO Demis Hassabis speaks with Tanya Lewis about how the team achieved this milestone, potential ethical issues and the most exciting possible applications.

A Good Memory or a Bad One? One Brain Molecule Decides

Quanta, September 2022

When the brain encodes memories as positive or negative, a small peptide called neurotensin determines which way they will go, new findings published in *Nature* state. As the brain judges experiences from moment to moment, neurons adjust their release of neurotensin. That shift sends incoming information down different neural pathways to be encoded as either positive or negative memories. As Yasemin Saplakoglu reports, the discovery helps illuminate how humans deal with conflicting emotions and why our brains may be evolutionarily biased toward remembering things fearfully. Scientists hope to harness this data and develop novel therapeutics for when this neurotensin system breaks down and negative processing dominates, contributing to anxiety, depression and addiction.

The Worst Pediatric-Care Crisis in Decades

The Atlantic, October 2022

Across the country, an early, massive wave of viral infections like rhinovirus, flu and enterovirus is slamming children and overcrowding emergency departments, Katherine Wu writes. Driven by low population immunity and receding COVID-19 mitigation policies, these pediatric patients are filling emergency departments and intensive-care units, overwhelming health providers. A look inside the packed PICUs dealing with this fall crush and how to prepare for a potentially more dangerous winter.

Racial Disparities in Maternal and Infant Health: Current Status and Efforts to Address Them

Kaiser Family Foundation, November 2022

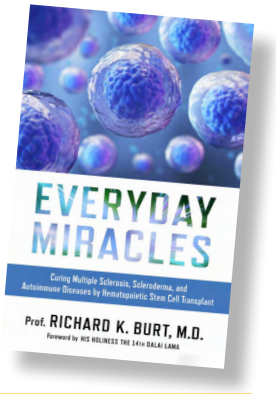
Across the United States, stark racial disparities in maternal and infant health have persisted for decades despite surging health care innovation and research. In this recent KFF report, experts explore how the COVID-19 pandemic and overturning *Roe v. Wade* are worsening these outcomes for people of color. Despite maternal and infant health disparities becoming more deeply entrenched, federal and state agencies and health systems are turning increased attention and resources to the issue, creating a potential tidal shift that could help reverse the negative trends.

Updates & Events

- On October 1, the world of obstetrics and gynecology lost a groundbreaking innovator when Beryl Benacerraf, MD, passed away due to cancer. A visionary ultrasound researcher, entrepreneur and physician, Dr. Benacerraf was a pioneer in the use of prenatal ultrasound to diagnose fetal abnormalities. The former professor of obstetrics and gynecology, reproductive biology and radiology at Harvard Medical School and Brigham and Women's Hospital authored over 280 peer-reviewed articles and conducted the original research that linked nuchal thickening to a heightened risk for fetal Down syndrome. Dr. Benacerraf was revered for her work and was honored in 2021 by the *American Journal of Obstetrics and Gynecology* as a "Giant in Obstetrics and Gynecology." She is survived by her husband, Peter Libby, MD, a cardiovascular specialist at Brigham and Women's Hospital, the Mallinckrodt Professor of Medicine at Harvard Medical School and a member of the Cura community, as well as her son Oliver, daughter Brigitte and three grandchildren.

- From November 13 to November 16, HLTH is hosting its annual conference for health innovation, pushing boundaries to transform the next decade of health. Across 100+ sessions, participants will hear from health and wellness leaders and senior executives tackling challenges throughout the entire health care industry. Speakers include Chiquita Brooks-LaSure, the administrator for the Centers for Medicare and Medicaid Services; Robert M. Califf, MD, U.S. Commissioner of Food and Drugs; Ara Katz, co-founder and co-CEO of Seed Health; Alexis McGill Johnson, president and CEO of Planned Parenthood Federation of America and others. Learn more and register at https://bit.ly/HLTH_2022.

- On November 15 and 16, *STAT News* is hosting the 2022 STAT Summit. The two-day event offers solution-oriented discussions into the most important topics in biotech, medicine and policy with leaders like Albert Bourla, DVM, PhD, Chairman & CEO of Pfizer; Chelsea Clinton, DPhil, MPH, Vice Chair of the Clinton Foundation and Nora D. Volkow, MD, Director of the National Institute on Drug Abuse at the National Institutes of Health. Learn more and register to attend the summit in person or virtually at https://bit.ly/2022_STAT_Summit. If you can't make it to the summit, drop by STAT in NYC: A Look Ahead at Biotech in 2023 taking place on December 5. Come for a look at what is ahead for next year and to take the temperature of the big regulatory and financial issues facing the pharmaceutical industry. Learn more and register at https://bit.ly/STAT_Biotech_2023.



- Congratulations to immunologist and author Richard Burt, MD, for publishing his upcoming book *Everyday Miracles: Curing Multiple Sclerosis, Scleroderma, and Autoimmune Diseases by Hematopoietic Stem Cell Transplant*. Alongside powerful patient stories, Dr. Burt shares his journey of developing the hematopoietic stem cell transplant treatment for autoimmune disorders. "These patients are the heroes," Dr. Burt has said. "Their bodies and spirits faced unrelenting disease, and yet they fight valiantly against the suffering and obstacles." Learn more and pre-order the book at https://bit.ly/Everyday_Miracles.

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