**The G Word Transcript**

**The Song of the Cell, An Exploration of Medicine and the New Human**

**Parker:** I'm Parker Moss, Chief Partnership Officer at Genomics England, and you're listening to The G Word. Through the conversations we have on this podcast, we hope to share the benefits of genomic medicine with everyone. Now, genomics is a word that can trigger really strong responses - hope, fear, anger - and there's a lot of information out there. But it's not all accessible to non-experts. We want to talk more about this word, The G Word: genomics.

Now, today we have a really special guest - a doctor, a scientist, an entrepreneur, a Pulitzer Prize-winning author - Siddhartha Mukherjee. His book, which I've been reading in Italy this summer, is just about to come out in October. The book is called 'The Song of the Cell: An Exploration of Medicine and the New Human'. We're covering some of the main insights from his book during this podcast and a few other scientific areas of research beyond. Siddhartha, welcome to The G Word.

**Siddhartha:** Thank you, thank you for having me.

**Parker:** Now, Siddhartha, you've got an incredibly busy life, and I'm going to just try to summarize all of the things that you do just for the sake of our audience at the start of this call. Tell me if I get this right. You are a professor at Columbia University. You were a former Rhodes Scholar where you trained over here in England at Oxford. You trained at Harvard, also at Stanford, and also at the Dana-Farber Cancer Institute. You trained first as an immunologist, and then as a stem cell scientist and finally as a cancer biologist before becoming a medical oncologist where you still practice today in New York, in NYC, having previously been on the staff at Mass Gen in Boston.

You're a scientist, a doctor, you have many authoring prizes, including a Pulitzer. You're an entrepreneur behind actually more startups than I could figure out in preparing for this call. You're also a husband to a wonderfully successful artist and sculptor in New York, a dad, and from what I understand, you also play jazz in a fusion band. Is there anything that I missed out?

**Siddhartha:** No, except for the fact that you should see me trying to ride a bike or trying to find directions, which I'm extraordinarily poor at. Actually, I think at some point in time, we'll find genetic markers that allow humans to find directions, and I will almost certainly have a mutation in one of them, or many of them. You can put me in a place that I've been to 1000 times before, and I'll get lost.

**Parker:** Well Siddhartha, I actually share that weakness with you. In everything else, you make me and most other people look bad by all of your achievements. Maybe just to start off, you could explain to our listeners how it is that you actually manage such a busy life. You are actually living really the lives of four people. I'd love to hear what a typical Tuesday afternoon is like for you, or even a Sunday morning.

**Siddhartha:** There's no magic answer. One answer is that I'm passionate about all of these things. That's why I do them. I do them because I like them. I like to write, I like to see patients, I like my science, and we do a lot of it. I like that science turns into medicines.

About four or five years ago, I decided that a major thrust in my laboratory was going to be the creation of new medicines. That's been very important because that's a different way of thinking about science. We don't do science projects for the sake of science projects. We do science projects, really, to create new medicines and to bring them to humans. That's what started the entrepreneurship journey. Now, I like to think about medicines. I like to think about human beings, and I like to help human beings in their suffering. Perhaps most importantly, I like the idea that science can be so profoundly helpful in all of this. A lot of the work is compartmentalized. I'll spend two hours writing, three hours in the lab, one hour with patients or two hours with patients, and the rest of the time thinking or doing whatever else, normal things that human beings have to do. It sounds like a lot, but the fact that they're so interconnected makes it actually part of one project as opposed to six projects. I'm not a ballet dancer who also happens to be making food at a restaurant. It's all part of one whole. That's what makes it seem as if I'm doing many things at the same time, whereas in fact, I'm doing one thing many times over.

**Parker:** I think that interconnectedness is the very reason you called your latest book 'The Song of the Cell', which is about the interconnectedness of cellular biology within the body. Maybe we should just go straight into talking about your book. For the audience who haven't read your previous books, your first book was called 'The Emperor of the Maladies', which is a brilliant biography of cancer. Your second book was 'A Gene, Intimate History', and your recent book, 'Song of the Cell'. Altogether, that's about 1,700 pages you've written. I've read all of them and I must say that your books are the most gifted present that I give people in my industry throughout. I have recommended them to many, many people.

This interconnectedness is one of the things that makes your writing style so attractive because you mix patients' stories and you're very generous with mixing your personal stories. You talk about science, but also science history, and the cultural ancient history of science, both from India and also the ancient origins of Western medicine. This seems to be a form of what has been successful, if you run throughout the theme of those three books. I'd love to hear a little bit about how you mix all this together and why it is that makes it so successful for the very broad audience that you appeal to.

**Siddhartha:** Parker, the most important piece of that is fascia, or the tissue of a book, is something that you have to think about before you think about the book itself. What does the book seem like? What is the mood of the book? What is the tissue of it? What is the fascia of it? It's almost like looking at a human being and asking the question, what's the whole before you start figuring out the parts.

I've never formally been trained in writing, but the way I started writing is by saying that I will move in my writing between very personal stories, the stories of my own family, the stories of my own discoveries. Between that, between very formal science which often contains a lot of jargon, big words, and also between that and the stories of patients. I won't compartmentalize them. It's not like one book is for patients, one book is going to be about me, and one book is going to be about the science and science writing. But all of this will be somehow blended together.

The hardest work for me in writing books is to find those connections, is to create that interconnectedness that makes a book whole. There's a very famous quote that the best technology is invisible. A pencil is an incredible form of technology because you don't think about it, you just pick it up and write. A hammer is a great piece of technology because you don't think about it, you just use it to bang a nail. If you have a piece of technology that is so complicated that you have to think about how to use it, where to use it, and what its application is, that becomes a problem. Books are like that, books are best when you move between spaces and forms of knowledge: personal knowledge, ancient knowledge, scientific knowledge, history, memoir, and so forth. Without you, without the reader realizing it, I'm going to take you on a journey. Trust me, that journey will go through many places, will go through my own journey, memoir, will span back a billion years in time when a particular kind of cell appears. We'll move forward into creating new kinds of cells and potentially new kinds of humans. But trust me, it'll all come out seamlessly if the book is good. It's those junctions, the junctions between those movements, those stories, that are the hardest to write, they take the longest to write. They are the places where my editors and publishers will really push the boundaries. That is, of course, very important. They work the best when they are invisible, like invisible technology. You won't know or you won't feel as if you moved through 3 billion years of time. If I can make you do that and still stay with me and trust me as your guide to this cosmos, the universe, whether it be cancer or genetics or cell biology, if I can keep your interest and trust, then I've been successful as a writer. The hardest thing about writing a book for me is actually not so much the content because I'm intrinsically interested in the content. The hardest thing is writing those junctional pieces that connect the book together.

**Parker:** Interesting. Again, we come back to interconnectedness, which, of course, is such an important theme of cellular biology, not just local but long-distance connectedness, as you described so well in your section on hormones. I have had so many sections of the book that I wanted to dip into. I've picked out a few that made the biggest impact on me, and I just wanted to share those with the readers and get you to explain a little bit further. Probably the first one is something that I know you have pinned to your office wall, which is the statement that a cell is a unit of life and physiology, but it is also the unit locus of disease. That seems to be a very important and fundamental insight, and I'd love you to explain the significance of that in the history of science and also the construction of your book.

**Siddhartha:** That statement comes really from Virchow, Rudolf Virchow's work. Rudolf Virchow's was a pathologist, his book 'Cellular Pathology' is probably one of the most important books in the history of medicine. Before Virchow, people were trying to advance or trying to understand unifying theories of medicine, and this has been a long quest. Is there a way to think about medicine, which is so diverse, or diseases, which are so diverse. You have autoimmune diseases such as lupus, you have infectious diseases, such as COVID, you have cancer, you have all these other diseases. Lots of people try to explain these diseases, illnesses, using various theories. There were theories that the psyche was the centre of all of this, there were famous theories that religion or spiritual dissonance was the centre of all of this. There were theories that there were invisible particles called miasmas, miasmata, that were the centre of all of this. Then Leeuwenhoek, a lot of colourful characters who you'll meet in the book, began to discover the cell and figured out that in fact, the whole human body and actually all animal bodies and plant bodies are built out of these units. These units are interesting, because they are simultaneously autonomous, they're living units, they have agency. They can do things, they have functions, but they also live together, they live in communities, which, of course, is the reason that you and I are made out of billions of cells. A small animal might be made out of 900 or 2,000. If the cell is the unit of us, and if everything, all of us, is built on cells, then what if normal physiology, the things that our bodies do normally, is actually a consequence of Cellular Physiology. It's what cells do to make our bodies happen. Our bodies don't happen by themselves. Our bodies don't happen magically. They happen because cells talking to cells, secreting substances, getting signals, making things happen, being functional is what makes normal physiology happen. That was the first insight and then he reversed it. He said, what if the opposite is also true? What if all illness is not some aberration of the psyche, or some visitation of fate from God, but rather is a dysfunction of some cell in your body? A malfunction or an infection or a disruption of the way cells should normally be behaving. In that second insight, he put together what I would call the first modern theory of disease, that all diseases are fundamentally cellular diseases and cellular dysfunctions. That's an incredibly astonishing insight, both of which normal geology and abnormal physiology tracking back to the cell just really sets the stage for the birth of modern medicine.

**Parker:** That is what set the stage for the first section of your book. You talk about the individual cells and then cells as a system, then cells as a locus of disease, and then you talk about Cellular Medicine. That is a large chunk of the latter section of your book. But I think you make a very interesting observation at some point in the book where you say, "Of course, every antibiotic is a Cellular Medicine and a drug that relies on the distinctions between a microbial cell and a human cell." In a sense, Cellular Medicine is not new, but it's being spoken a lot more today with cell and gene therapies. Maybe you can explain to our listeners what has changed in recent years that has created so much excitement and enthusiasm, both from scientists and also the investment community in cellular gene therapy.

**Siddhartha:** For the longest time, we were intervening on molecules resident in cells. An antibiotic is a great example. It blocks a molecule that's essential for the life of a bacterial cell, whatever that molecule might be; it could be a ribosome, which makes proteins; it could be the enzyme that makes a cell wall for a bacterium, and so forth. But more recently, we've started by doing things that are actually very radical and very different. We're not just thinking about making small molecules that go and drug one piece or parcel of itself, although those are still important. It's not that the importance has gone away. Recently, we've started doing things like putting cells into human bodies, growing the cells outside the body, and putting them back into the body, or changing the behaviour of a cell in total such that previously, an immune cell was previously ignored, a cancer would suddenly start recognizing that cancer. The more recent developments have been in changing the behaviour of cells and implanting or transplanting cells.

**Parker:** In fact, you have gone further in your personal research than just changing cells and reimplanting them in the body. I remember when we first met for lunch in London in 2018, you were telling me about some experiments that you were doing with Ron Vale and monocytes, and I was really excited to hear that. Discuss a little bit further in your book. In this particular case, you were making a chimera out of a monocyte and transforming it into something resembling a little bit more like a T-cell to fight cancers. That is an absolutely fascinating idea, and it will give you a chance to talk about your life, not just as a scientist, but as an entrepreneur. I'd love to hear a little bit more about how that experiment and that company is going.

**Siddhartha:** First of all, we've already dosed a few patients. In the three years since we had a conversation, that has grown into a real therapy. It has gone through FDA scrutiny, and we are dosing patients. We call them CARMs, chimeric monocytes. The other idea that we spoke about has been now published. Let me take a step back actually, this is an interesting step back. In a fundamental way, even though I wrote the book 'The Gene', I sort of either willingly or unwillingly missed the genetic and genomic revolution. By saying that, what I mean is that I was always interested in, obviously, genetics and genomics, but my lab, as an in my lab practice, that was never my primary interest. I was never interested in doing multi-genome sequencing and then computational stuff that comes with it, which I think is very important. It was just not interesting to me because I was more interested in the whole organism in organism and biology. A gene, as you know, is extraordinarily important. It's a carrier of information. But it's lifeless. Without a cell, a gene is a molecule, a cell brings it to life. My laboratory really focuses on things that are not genomic but are cellular. The distinction is again, the fact that we, of course, are interested in genes and interested in what genes do and how they work. But we don't do a lot of multi-gene sequencing, the kind of things that other people do very well, but we don't. My thought was that rather than focusing on the genome, why not focus on cancer's physiology? I began to think more and more about cancer as an organ and ask questions like, any organ, how does it consume nutrients? What is its environment? How does it make a home for itself? How does it create three-dimensional structures for itself? Why does it move around? How does it move around? Could those be new targets of therapy? We, for instance, published a paper with Lewis Cantley on how cancer metabolizes sugar in the presence of insulin. And what's interesting about that paper is that we believe that's also a uniform the company, and is now in trials, we've just started treating patients with this diet drug combination. The company is called Faeth, but then you know, all of us believe that we've sort of missed out on using cancer metabolism as a locus of therapy. So that would be one example. But there are others.

**Parker:** How fascinating! Maybe you could answer this, having lived on a cancer ward myself for five years: one of the most persistent kinds of patient-led theories is that sugar is essential to the metabolism of cancer. And if you starve the body of sugar, that can bring you back into remission. It's something that I've had doctor after doctor dismiss. Could there be some truth to this?

**Siddhartha:** I think there's a misconception here, which is that cancer certainly utilises sugars differently than normal cells. We know this from work done by Otto Warburg in the early part of the 1900s. But that doesn't mean that cancer is, you know, that if you stop eating sugar, your cancer is going to go away, or that eating too much sugar causes cancer. Those are two misconceptions. What's true is that the pathways by which cancer is consumed sugar, and especially the pathways by which cancers sense sugars, which is through insulin, the central hormone that coordinates sugar metabolism, those pathways can be potential targets for drug therapies. In the end, whatever diet you eat, if it contains carbohydrates, it will, in the end, convert those carbohydrates into sugars. And cancers will eat them, will consume sugar because all cells require sugar as glucose as a central metabolite. So it's a misconception that you can, quote-unquote, starve your cancer by not eating sugar. But it is not a misconception to say that you can target particular vulnerabilities that cancer cells have in their dependence on particular ways that they digest and sense. And those can be drugged. And those drugs can be successful if you can starve the cancer simultaneously. And that's what we're doing.

So, my recommendation is don't go on some crazy diet. That's not the way it seems that cancers work. But more appropriately, there are scientific ways, which we're now discovering, by which the dependence of cancers on particular kinds of ways that they digest and utilise sugars can be made into vulnerabilities that can be exploited for the treatment of cancer.

**Parker:** Okay, well, thank you for clearing that up. I think that will be of great interest to the cancer patients who are now tuned into this call. So, my next question - I hope this works - I want to find a bit of interconnectedness between the cellular biology, the genomics that you mentioned just before, and then some of the, what I thought was the most beautiful metaphor that you brought from ancient Indian religion. And so, I'm going to read a quote from your book that I found very moving. So, this was a quote about Yashoda, the mother of Krishna, who was one of the major Hindu deities, and at one point, she opened his mouth because he had swallowed a clod of dirt. And when she peers inside, she sees his teeth, and they have been witnesses to the whole universe inside of him - the stars, the planets, the million suns, the whirling galaxies, the black holes - and then you make the connection that with each of our B cells carrying a reflected cosmos, the cognate reverse of every antigen in the universe. And what you're referring to here is antigen presentation, so important for immune oncology, and, of course, highly connected to genomics. This has been discussed a lot recently in the context of the so-called cancer therapeutic vaccine. And I'd love to hear your thoughts on where you think we're going with MHC with antigen presentation and whether, indeed, you feel that sometime in the next five years, we may be able to recognize these new antigens and drug them.

**Siddhartha:** There are many questions in that, but let me start with the historical perspective. The problem of antibody, so as you know, antibodies are proteins that are generated in your body that can bind to viruses and bacteria floating in the blood or to cells, proteins that are outside cells. They have to be visible in the blood, or the lymph nodes, and or in the tissues, and antibodies, you know, are like pitchforks. In fact, they really resemble pitchforks, and they go and attack them like missiles or like pitchforks and then summon a whole cascade of other cells to come and kill the end other proteins to come and kill the bacteria or the virus, or a cell if it's important for if it's recognized as a foreign cell.

Now, there was a big debate, a huge debate in the 1960s going on into the 1970s whether it, because the funny thing about antibodies is that how would you ever know every virus or bacteria that ever attacked you? You know, there's a new strain of flu that's going to come next winter, and the question is, how would your body know? How would your B cells which make the antibodies know that this was a foreign object, this was a foreign virus? Similarly, for other viruses and bacteria, so one proposal was that the B cell had a universe of everything in its body, in itself, in its genome, and that universe was being somehow deployed or parts of the universe were being deployed to kill the new strain of influenza or the new strain of a virus or whatever it might be, a foreign cell. But this is like Krishnas blob of dirt, you know, that the B cell had the entire cosmos of everything that could possibly exist in the universe that would then, you know, when that thing came along, when their foreign body came along, the visa would say, "Aha, here you are," and "I'm going to now send out my antibody from my repertoire to come and kill you." But of course, that doesn't make sense. How can how can a B cell which How can any cell have the information about the entire cosmos, not just a bacteria that that exist in the world, but strains of influenza haven't even been born yet that will only come in the future that wouldn't exist? It doesn't make sense. And the answer to that lies in the fact that B cells learn. And by learn, I really mean it is a Darwinian process by which they're selected. And the B cells basically take their genomes, the genes, rearrange them, and make and a very important one here, they make a new antibody, a receptor that becomes an antibody against this new virus. And they learn, they have this adaptive capacity to thereby secrete an antibody against a new pathogen. But it was a fascinating discovery that the B cell did not contain a universe, but it rather learned a universe as it went, as a new pathogen came along. So that's the answer to the first part of your question.

The second part of your question is, can we utilize this knowledge? T cells also have a variation of this. Can we utilize this knowledge to make new cancer vaccines? And the answer is absolutely yes. If we can find determinants in cancer cells that are new, that are different from normal cells, we could potentially unleash the immune system on them. This has already been done or being done. And, again, is the basis of one of the things that my lab is doing very actively, looking for these so-called new antigens, things that are on cancer cells that are not on or inside normal cells, and then trying to unleash an immune response against them.

**Parker:** So if your lab is highly engaged in that, I presume that means you've turned the corner and you are getting much more involved in whole-genome sequencing, which is actually the business of Genomics England over here. And I would love to hear a little bit of your thoughts, given this is really a genomics podcast, about where you feel not just how genome sequencing but also kind of other multi-element technologies like transcriptomics, proteomics, and long-read sequencing are playing into the lab of the future and whether you're exploring those other modalities together.

**Siddhartha:** We certainly are, our take on this has been, as I said, we've entered genomics cautiously and carefully, not because I think it's an incredibly important technology, but because it's a very crowded field. My laboratory does work that is adjacent, and we use collaborators to do our genomics. So this work of discovering new antigens for us is really proteomics and AI. So we've engaged a lot of proteomics and AI folks to try to discover new antigens and create therapeutics against them. And we rely a lot on whole-genome sequencing to once we found what this new antigen is, we rely a lot on both genome or exome sequencing to figure out where the genome is coming from, how it's expressed. So that's transcriptomics, looking at the RNA sequencing, and trying to figure out the biology of why it's a new antigen, and how new antigenic is it? Is it really present only in cancer cells? But is it also potentially present in some other cells that we want to unleash the immune system against something in the cancer cell that was also present in a vital normal cell?

**Parker:** Okay, thank you. Well, I mean, this was not your book about cancer. You talked about many other areas of cellular biology. You talked extensively about insulin production in the pancreas. One of the areas that I found most moving in your book was your discussion of cellular neurology and neuroscience and you did something which I've noticed you've done throughout your books, which is you've infused not just the history of your patients, but some of your personal history and family history. You were very open that you experienced depression at one point in the past and knew very movingly described depression as a flaw in love. And then you went on to make some very interesting insights about neurology and advances in that space. I'm wondering if you could just talk a little bit about how your lab engages in neurology today.

**Siddhartha:** You know, we're not in a neurology lab. We don't work on neurology, and hopefully, one piece of biography that you left out, which was very well known actually, is that for a time, I was actually trained in neurology and neuroscience. I worked in Connie Cepko's Lab. Connie remains a very close friend, and she's of course, a great neural cellular neurobiologist. I wanted to write that section on depression not just to highlight some of my own history and struggles with that illness, but also to describe to the people the idea that depression is being more and more understood as a workout would have, not merely as a psychic disease or a psychic state, but really as a disease of cells and cellular circuits. And that's a very profound change because, again, you know, for years and years, you know, 50 years ago or 100 years ago, before our understanding of deeper cellular science, people would say depression is, you know, a set of circumstances, environmental circumstances that cause your brain to feel or your body to feel bad about many things. And it is reflected in multiple behavioural changes, etc., etc. If you went and sat on a couch with Freud in Austria or in London, you know, and you said that you were depressed, he would likely explore your traumatic history, potentially your sexual history, your behavioural history, and so forth. And all that still remains true. But what I wanted to highlight in that section was that all of that said, it is also a disease of cells. Because every disease is ultimately, as going back to work out, is a disease of cells. And understanding that cellular basis of why mood is right, or why and how mood is regulated, creates profound new forms of therapy, including antidepressants, including new antidepressants if you haven't even begun to explore that we're just beginning to explore.

People like Paul Greenguard, who passed away, was very interested in new kinds of antidepressants which would not just be serotonin inhibitors, which are most antidepressants today, serotonin uptake inhibitors like Paxil or Prozac, but new kinds of antidepressants that would act on the cellular pathways that regulate mood but also potentially electrical circuits. You know, there are people I described in the book, there are people in whom electrical stimulation of circuits is being used to relieve the most profound forms of depression, recalcitrant depression. So there is a whole new universe of antidepressant therapies that are coming that rely very fundamentally on our understanding of how mood is regulated in the brain. What neurons regulate mood, what hormones regulate mood, how those neurons and hormones interact with each other and ultimately impinge on mood-regulating cells and cell circuits, which I think is and could be radical and very different from, you know, the way we thought about depression 50 years ago.

**Parker:** I found that section of your book fascinating and very moving, and maybe there's just one other section I really feel that I should call out given that we are in mid-2022, which is your short but important section on COVID. And you observe that there is a bit of a triumphalist narrative about how the scientific community responded to COVID, but also there was a very humbling reminder of our lack of preparedness. And I know COVID was a difficult time for you both as a doctor and a scientist. I'd love to hear a little bit about your experience during these last two years and the impact it's made on you.

**Siddhartha:** Well, I think, as I said, that triumphalist narrative is well known. You know, we knew it. We now know or knew enough about cell biology and vaccines and the immune system to be able to develop a vaccine against the disease, a pandemic, a global pandemic, in record time. I mean, you know, the last vaccine that was made this fast was made against mumps, and it took, if I remember correctly, about four years. In this case, we had a vaccine in six to eight months. So that's a triumphalist narrative. But there's another humbling narrative behind all of this, the humbling narrative and all of that, two humbling narratives. One humbling narrative is about politics and preparedness, global preparedness. That's not a cell biological narrative, but it's an important one and maybe at some future time, I've written about it in The New Yorker and you know how we didn't have enough preparedness in every way to meet a global pandemic. But there's also a humbling cell biological narrative that we need to understand, which is that even today, if you ask the world's experts on COVID, you will come to the realization that there are things about COVID that we still don't understand.

Why is it that this virus could cause this kind of very diverse pathology? You know, very mild infections in some people, extraordinarily lethal infections in others? What is long COVID anyway? And why does the virus cause long COVID? Why did the immune system fail to clear COVID, which is a part of a family of viruses that cause the common cold, and you know, we take care of the common cold by, you know, chicken soup, and yet a distant cousin of that same virus was able to cause a global pandemic. Why? What about the immune system? And the insights that have come out of that have been really quite profound.

I'll give you just one example of them. It turns out that many people who suffered very severe COVID, for them, it was because COVID didn't trigger the appropriate immune response. Because COVID was able to subvert the immune response of some people. And what's really astonishing to me is that the reason that COVID could subvert the immune response was that it was basically that these people had had an autoimmune disease, previously unrecognized autoimmune disease, that made them susceptible or vulnerable to COVID ability to subvert response. It boggles the brain to figure that out. But it turns out to be true that, in fact, some of us because of genetic reasons, and we will notice as we sequence more and more genomes, some of us because of genetic reasons, aren't able to play out the early alarm bell when a virus like COVID infects our body. Some of that is because of genetic reasons, some of that is because we have an autoimmune reaction but we don't know it. We don't know it because such a virus didn't come before. And so it's a very humbling idea that there is so much more to be discovered about the immune system and about how the immune system reacts to viruses that we've sort of gone back to the drawing board and began to ask questions. I mean, maybe this is true for many other viruses we just didn't know it because, as I said, there wasn't a global pandemic of this sort and there wasn't focused attention of this sort on a single virus and how it interacts with the human immune system. Maybe influenza causes some syndrome that we haven't really followed up on, maybe Epstein-Barr Virus causes a long Epstein-Barr Virus syndrome that we haven't really fully understood yet because we haven't looked properly. So it's been a really humbling experience, I think, for cell biologists, and immunologist in particular, to realise that, you know, we thought we knew so much about the immune system, it was one of the most mature systems that we knew about. And then now discovering that, in fact, we don't know everything about it. And many, we don't know many things about it.

**Parker:** Yeah, that's a fascinating explanation. And it's an area actually that Genomics England has been very involved in and I can share some papers afterwards. But we did what we think is one of the world's largest host sequencing programs.

**Siddhartha:** I'm very aware of it, yes,

**Parker:** Your aware of that - wonderful, and we found some interesting features - interferon alleles, which were very different and drove some susceptibility, and also sort of severity of response differences.

**Siddhartha:** And the fact that that's very interesting is that, you know, this is what makes science very satisfying. Is that you come at it from a genomics angle, or rather, Genomics England comes at it from a genomics angle. Immunologists come at it from an immunological angle. You know, I come at it from a cell biological angle, and all of these angles seem to be converging. They seem to be converging on, for instance, proteins like interferons, and the interferon response, early interferon response, as being one of the predictors of why people have severe or not severe COVID. The fact that these three very different approaches, or four, very different approaches, really converge on the same idea, really gives credence to how science works and also gives credence to the idea that the thinking, of the science is probably right.

**Parker:** Which comes back to your beautiful book titled "The Song of the Soul and the Interconnectedness". So, just a few quick-fire questions as we begin to wrap this up because there are so many other things I'd love to ask you. First of all, in a footnote in your book, you gave a hint towards a new edition of "The Emperor of Maladies". Can you give us a little bit more of a taste of what might be coming?

**Siddhartha**

Well, you know, I think that broadly speaking, obviously 10 years have passed, a little more than 10 years have passed since the publication of the book and we've made many advances. There are advances in prevention, in early detection, and treatment. In prevention, we've begun to identify new potential ways that we can think about cancer and preventing cancer. The whole idea of inflammation, obesity as being potential, I would say, sort of internal carcinogens, is a fascinating idea. We always talk about carcinogens as chemicals or things that came from outside, but that your body's internal milieu might be pro-carcinogenic or pro-cancers is a new idea and there's been a lot of work done on that, and work continues to be done on that.

So in early detection, again, this is an area where genomics plays an enormous role, in not only classifying patients and screening them, for instance, finding genes or combinations of genes that put you at high risk for breast cancer, whether those patients should be screened more aggressively for early breast cancer or ovarian cancer and other cancers, and also the possibility that we could use genetic techniques, such as when cancers spill their genetic material into the blood, they could be picked up, and thereby identify cancers in an early stage. What that would do as we move forward in cancers, and in the treatment space, the biggest advance has been, I think, immunology and an immune system detection of cancer.

So that's just a brief taste of how these chapters now, but of course, they're not really written out like a textbook, but rather, as the "The Emperor of Maladies" is written, sort of in a series of stories. Stories of patients, stories of people in these three very broad spaces prevention, early detection, and treatment of cancer.

**Parker:** Well, I will be going back through the whole book when you bring out the second edition. I read it about eight years ago, and I definitely need a refresher. And another thing you hinted about, which I wasn't aware of actually, until finishing the Song of the Cell, is that these three books are part of a quartet. Can you explain that final bit of interconnectedness to us?

**Siddhartha:** Well, I think the last book in the quartet is going to be about metabolism, longevity, ageing, and death. This book is finished, of course, but I’m in the middle of publicising this book, so I haven't had the brain space to think about the fourth book. But I will start writing it, I think, maybe in a month or two, once I've sent out a couple of important scientific papers from the lab.

**Parker:** Well, it's clear that these books pour out of you and it's remarkable that haven’t really launched you’re third book and you're already planning your fourth one. So, you mentioned before, early detection, and this has been much talked about in the UK because, as I'm sure you're aware, we are running a major 140,000 person trial with Grail's technology. The NHS, not Genomics England, but we're following it closely. And I suppose as a doctor, I would just love to hear your vision of the future. Can you see a time in the next five years where every adult will take a blood test every year and look for methylation markers to detect early signs of burden of cancer?

**Siddhartha:** Well, I think that I think the broad answer is yes. But the narrow answer is that it's going to take up it's going to take very heavy lifting. And I'm very proud of the NHS and its efforts to do this because it requires a whole system to achieve this. And it really requires a centralized system like the NHS. You know, there are many, many, many questions that will have to be answered. For instance, is it true that there are some cancers that are detected in the blood, which will never become real cancers? They're just going to sit there and never do anything to you? Will this technology save lives? Will this technology over detect cancer? And thereby cause, you know, all sorts of extra work and the economic consequences of the work? Or will it be the opposite? Will it be a transformative technology in which we detect cancers at a stage where, you know, they can be curable by just cutting them out? How accurate is the technology? How quickly can it detect the cancer? But most importantly, can it tell us where the cancer is? You know, you can detect a cancer mutation in the blood, and then you go searching for where the cancer is? What if you find the wrong place? How certain can you be that that cancer is the one that's triggering that detection? So I'm very excited about the study but I know that there are many, sorts of what I would call narrow roads to cross before we can make a broad announcement that this is going to be a mechanism by which we can detect cancer early.

**Parker:** Okay, I only have two questions left. My penultimate question is really something for many of the cancer participants of the Genomics England programme who I know will be tuning into this and these are people of living with cancer today or parents of children with cancer. And I would be very interested to hear what you think should make the cancer patient of today hopeful for the future?

**Siddhartha:** Well, I think all of these things, you know, prevention, early detection, the use of immune therapy, the birth of novel drugs, potentially the birth of combination targeted drugs, should make patients hopeful. We are trying, I think, our best to understand, but also now to use that understanding to treat cancer, and we've gone from genomics to cell biology to organismal biology of cancer. And I think that is yielding new drugs that we hadn't seen before. So I'm super excited about it, and I'm eager to learn about, you know, what the next steps are?

**Parker:** I feel the same way, and I must say that I think I would really commend all three of your books to patients of cancer, rare disease, or any other disease out there because as well as educating any reader of any level of scientific training about the history and the scientific nature of the disease, it also, I think, communicates very well to the reader the white heat of the furnace of energy from scientists like you Siddhartha, who are working day and night to cure these diseases. And I think sometimes being on a cancer walk can be a lonely place, and it is encouraging to know that there are people like you working long hours to try to change the way we can address these diseases. On behalf of all of the cancer patients and the rare disease patients that we represent, thank you so much for all of your energy and investment in this space it is truly a remarkable story.

**Siddhartha:** Welcome. Thank you very much. And, you know on my end, all I can say is that I'm really excited about what Genomics England is doing. I'm excited about this NHS collaboration with GRAIL and you know, I think this is the kind of thing that we require - these kinds of massive pushes to fight this complex of nefarious diseases that have plagued human beings since the very birth of humankind. So, I'm happy to be part of the journey.

**Parker:** Thank you, we are certainly working hard on it over here as well. And my very last question to you, which I ask all of the people that I speak with, who would you recommend I speak next to on the G word?

**Siddhartha:** Well, you know, a couple of people come to mind. I'm, I don't know Bert Vogelstein personally well, but Bert's been there from the inception of genomics for cancer. He was among the first to discover cancer genes and among the first to discover the fact that cancers didn't just arise out of nowhere but sort of marched slowly, progressed slowly towards cancer. So, Bert comes to mind.

Ruslan Medzhitov, the immunologist at Yale comes to mind. He's been exploring the innate immune system, and his wife, a very accomplished scientist, Akiko Iwasaki, who's also in the book, an expert on COVID comes to mind and the genomics of Covid. She is running, I think one of the most fascinating long COVID studies that I've encountered. Finally, someone from your own neck of the woods, Nick Lane, comes to mind. He's not a genealogist in your sense of the word, but he explores evolution, from the birth of very early life forms to questions about what is life, how is life created, and what were the earliest forms of life. I interviewed him for my book and found him fascinating about some of these questions. So those are some names I would throw out.

**Parker:** Those are three wonderful suggestions. Thank you so much Siddhartha and for my listeners, that's all for this episode. Thank you so much for listening to this discussion about the G word and for joining us on this journey to highlight and debate the implications of genomics as it comes to the mainstream of healthcare and society.

If you have any views on these topics, or have a person in mind you'd like us to interview, do please write to us at podcast@genomicsengland.co.uk. We really appreciate your support. And most of all, I really appreciate your time today. Siddhartha, thank you so much for joining us on the G word.

**Siddhartha:** Thank you. And thank you and good luck.