

Road to Resilience Transcript— Stronger for Longer

Healthspan Matters

Stephen Calabria: [00:00:00] From the Mount Sinai Health System in New York City, this is Road to Resilience, a podcast about facing adversity. I'm your host, Stephen Calabria, Mount Sinai's director of podcasting.

Most of us spend very little time thinking about aging until it starts affecting our daily lives. Maybe it's taking longer to recover from an illness, maybe it's a chronic health condition that's become harder to manage, or maybe it's the realization that living longer and living well aren't necessarily the same thing.

Scientists are increasingly focused on what's known as health span, the number of years we remain healthy, active, and resilient. It's a shift from asking how long we can live, to asking how well we can live.

And answering that question means understanding some of the most fundamental processes in human biology, including the immune system, metabolism, and the ways our bodies change over time.

Today we're joined by Dr. Daniel Puleston, an assistant professor of immunology at the Icahn School of Medicine at Mount Sinai, and a member of [00:01:00] both the Precision Immunology Institute and the Tisch Cancer Institute.

Together we discuss health span, resilience at the cellular level, and what today's science may reveal about staying healthier for longer.

Dr. Daniel Puleston, welcome to Road to Resilience.

Daniel Puleston: Good to see you. Thanks for having me.

Healthspan vs Lifespan

Stephen Calabria: So we're here to talk about healthspan. To kick us off, what is the difference between healthspan and lifespan?

Daniel Puleston: Lifespan is the number of years that you live, right? The number of years that you're alive.

And healthspan is essentially the number of years that you live well And I think the reason why this is becoming more and more into the public consciousness, this idea of healthspan, is because these two numbers are expanding, right? In terms of the difference between our lifespan and our healthspan.

We've made really great strides at improving lifespan and longevity over the last century. So vaccination, sanitation, antibiotics, understanding cardiovascular disease, [00:02:00] stopping smoking.

Have done a really great job of extending the number of years that we get. This is a huge win over the last century or so, certainly since nineteen fifty.

But the consequence of that is whereas someone now might have passed away at sixties living to eighty-five, 'cause we have these interventions, these new understandings, but now the extra years that they get, they might be living with diabetes and cardiovascular disease, decline in cognitive health.

And the kind of goal when we talk about aging and longevity and healthspan is really minimizing the difference between your lifespan and your healthspan.

I think conceptually the idea is you live as long as you can, really healthy, and then you metaphorically fall off a cliff and you pass away. That's, a bit morbid to say, but I think this is all of our preferred kind of path.

Whereas what we have right now is this slow decline at the end of our life into ill health. And in the developed world, that equates to about ten years at the end of our [00:03:00] lives when we're in meaningful ill health.

And that's a significant amount of time, right? We don't want the end of our lives to be the most challenging if we can avoid it. So this is the kind of the essence of healthspan, how long we live well for.

What Aging Can Change

Stephen Calabria: To some extent, I imagine a certain measure of that decline, though, is inevitable. How much of what we accept as just normal aging is actually something science may be able to prevent, slow, or even better manage?

Daniel Puleston: Yeah, I think there's a few things to that. So one is we already have pretty good mitigation strategies for some consequences of aging. So let's take cataracts. People get cataracts when they get older.

This would have been a burden on people's lives. Now you can go into an outpatient clinic and have them whipped out in thirty minutes, right? Statins.

Cardiovascular disease was this huge burden in our lives before we had these medicines, and now they make what is potentially a really serious disease, is a serious disease, more manageable, and these are routine things, right? A

[00:04:00] statin.

Orthopedic surgery. If you fall and you break your hip, you can go and have a hip replacement.

So we already have things that can mitigate the consequences of aging, some consequences of aging. And I guess the other side of that is what can we do to intervene? What other things can we do, right? And I think this is where we get at behaviors, and there's behaviors that you can do. So exercise- Ugh.

I know.

Stephen Calabria: I knew it was coming.

Daniel Puleston: I know. I feel you. I feel you. That Orange Theory membership, I'm not sure it's worth it. But exercise weightlifting, honestly your kind of muscular tone and strength nutrition, sleep, stress, right? These are the things.

We can engage in these behaviors to mitigate some of the effects in aging in our advanced years. And then, and perhaps we can talk about why the, why those things work. But I think also what you're getting at is, can we get at the drivers of aging, right?

Is there things that we can do to really slow the pace, perhaps with a pharmacological intervention or with a pill or with a drug? And the answer to that, sadly, right now is no. We have an understanding of what the drivers are.

Our understanding is not [00:05:00] complete, but we have an understanding of what the kind of mechanisms are, what the, what's happening with the biology, what things are declining, what things are changing.

But whether we can intervene in a human being and give them something which is gonna act as some magic slowing or curing of aging is, we don't have that yet. We know how to do it in mice.

We know that calorie restriction or if you give them spermidine or rapamycin, we have this understanding.

But we don't know if this translates to a human being yet. It's not that it can't or that it won't, it's just that we haven't done those studies yet to really understand if they can. So this is kind of where we are, I would say.

Immune Aging Early Signs

Stephen Calabria: From an immune system perspective, what are some of the earliest changes that begin affecting our physiological resilience long before we even recognize them?

Daniel Puleston: The immune system is so important to the way we age. I think one of the really fascinating understandings that we've come to glean over the last five years or so is that an aged immune system and an aged blood is sufficient on its own to drive aging.

So the only thing about you is that you have [00:06:00] an aged immune system. This is enough to age your liver and your kidney and your brain. So the aging of your blood is very significant to the way that we age in total and systemically.

And there are parts of the immune system, to get at your specific question, that change quite early in our lives, begins to decline early in our lives. And one example of that is the thymus.

So the thymus is this organ which sits above your heart. Fascinating organ. Some amazing things happen there. But essentially what it's needed for is to generate immune cells, a particular type of immune cell called a T cell.

And T cells are important 'cause they orchestrate our immune response, and they are the cells which are responsible for killing cancer cells and virally infected cells.

So a very important cell for us. This organ maximizes in size and in its function in puberty. And from then on, from puberty down, it declines. And by the time

you hit 40, that tissue is largely just fat. It's not doing anything of function. I'm 40. I don't feel like I'm old, but yet I have this kind of aged organ [00:07:00] in my body.

And by the time you're 70, it's largely not functional at all.

Stephen Calabria: It's basically your appendix at that point.

Daniel Puleston: Yeah, it's really not doing anything. And so you're no longer generating these new immune cells. And you don't feel it because you're living off and sustaining yourself off all of the immune cells, the T cells that you generated when you were a kid and when you were a younger adult.

So you don't feel it for most of your life, that this organ is shrinking and withering away, but it becomes consequential in later life.

And so, the problem with when you're not generating new immune cells every day, 'cause normally the other cells of the blood, you're pumping out new ones every day, is that you become slightly less adept at responding to new things.

So new viruses, new vaccines, maybe a new cancer cell that crops up, and you have this kind of loss of immune competence a little bit because of this. So that's one thing that changes really early and gets worse as you get older.

Chronic Inflammation Explained

Daniel Puleston: Another thing would probably be chronic inflammation. We know that chronic inflammation is a hallmark of aging very important driver of aging, [00:08:00] and that your level of chronic inflammation slowly rises as you get older.

But you can't feel it. You're not really privy to that.

Stephen Calabria: Define inflammation. I think of inflammation, I think of a flame.

Daniel Puleston: Yeah, so inflammation, perhaps another way of putting it is activation of your immune system. All right? Your immune system is active in some way, and an immunologist would call that inflammation.

And so inflammation is a totally natural process. When you have a flu infection in your lungs, you have inflammation in your lungs. That inflammation is your body and your immune system responding to that infection.

Stephen Calabria: I would think that's a good thing. That your immune system is inflamed and fighting off bad actors, as it were.

And when you're healthy it's totally a good thing for the most part. It can make you feel sick, and, the reason why you're on the sofa and you've ordered your pizza and you're watching a movie is because you feel a bit crappy, and that's actually your immune system, your inflammation, which is making you feel that way.

It's trying to make an uncomfortable environment for this bug that's inside you, right? But inflammation can be bad, if it's present when you don't [00:09:00] want it to be, and we see this in kind of autoimmune diseases. This is when you have this unwanted inflammation, which is present at the wrong time, right?

And it is, it's sustained long after you needed it to be. But in aging, we have what's called this chronic inflammation. So it's low level. You are not privy or cognizant that it's happening, but it's there. You can measure it some degree in your blood, and some of these inflammatory proteins in your blood increase as you get older.

And it's an interesting concept because one might think, "Okay, you have a bit more inflammation. Is this a good thing?" Maybe it's a good thing. Your immune system's more ready.

But what happens is that even though you have slightly more immune activation, your immune system is not very good at ramping up when it needs to. So you can think of it like an alarm that's giving you this slow whine, but doesn't go off when the intruder comes in.

So this is what's happening to your immune system. You have this low level chronic inflammation, which is driving aging of your tissues and is not allowing you to [00:10:00] activate appropriately when you want it to activate properly.

So you don't feel this as you grow older, but it becomes consequential later in life because when you need this kind of short burst of inflammation you're less good at inducing this.

And with this podcast being called Road to Resilience, I imagine that low level inflammation, that alarm constantly going off that you don't really hear half the time, that has a negative consequence in the long term on your body's resilience.

Daniel Puleston: Yeah, inflammation is, sustained inflammation is incredibly damaging to the tissues, right? It causes damage to your cells. It can cause damage to your DNA. Sustained inflammation has a risk associated with cancer, right?

So a lot of patients who have autoinflammatory disorders, in those sites where they have that inflammation, there's a heightened risk of developing cancer.

So it's highly consequential to the way that we age and to our risk for disease when we have this chronic inflammation.

Why Habits Work

Stephen Calabria: In recent episodes of one of Mount Sinai's other shows, The Vitals, we did a Healthspan miniseries, which [00:11:00] featured some of our dear friends, Doctors Miriam Murad and Shruti Nayak, and I encourage our listeners to watch.

The experts talked about exercise, nutrition, sleep, and stress management. Could we get into a little why these seemingly simple habits remain some of the most powerful tools we have for improving healthspan and perhaps even warding off chronic inflammation?

Daniel Puleston: Yeah. That's a, it's a really good question, and I think we think of them as simple because they're so familiar to us.

They're things we do all the time, and they're easy to say, but the, the effects of doing them are not simple I think for many people we have this idea, maybe we touched upon this earlier, that wouldn't it be great if we could have one pill that we took and it stopped us from aging? But that's-- maybe we will have that one day, but that feels like a fantasy right now.

Because often when we take a pill and we take a drug, it's targeting a very narrow part of our bodies, right? It's targeting a specific protein or a specific pathway. [00:12:00] And aging is this complex event that happens as we cumulatively, as we get older, which affects all of our body systems. So it's this system-wide thing.

It's affecting how our organs and our tissues are interacting with each other, what's going on with e- within each individual organ. So it's unlikely that there's gonna be a single pill that targets a single thing that's gonna give us this magic bullet of slowing everything down. But what exercise does, and nutrition, and limiting stress, is it has system-wide effects, right?

This is a way that we can actually impact multiple tissues, right? Multiple biological pathways. So take exercise. You work out, you go to the gym, you have a gym membership, right? You're doing lat pull-downs, whatever it is people do in the gym, and you're increasing your muscle mass, so you're becoming stronger, better muscle tone, which when you're older means less frailty.

You have more muscle, which means you have better systemic metabolism, because the muscle, along with your liver and your fat tissue and some other places, [00:13:00] are the things which regulate your global metabolism.

So now you've got better systemic metabolism. Every time you work a muscle, you're releasing some molecules into circulation that can act on the liver and the brain.

So you're getting all of these really systemic effects from doing this very simple thing. And the other interesting thing is that these things like exercise and nutrition, in terms of their anti-aging effect, often they converge on certain pathways that are very important for aging. And they reach pathways that these drugs that we're all trying to develop as anti-aging are trying to target anyway.

So, you can get there without taking the pill and having that side effect and, without having to do all these clinical trials. We already know how to target these pathways important for aging through these mechanisms, right? Through these behaviors.

The problem, of course, is keep, keeping up with them, right? Amongst a busy life, it's so difficult to exercise regularly and eat well. Of course, this is the challenging thing.

And then the one last thing I would say is [00:14:00] that, which perhaps a bit more of a philosophical point is that let's take sleep, which we know when you're sleeping, you're clearing away a lot of the damage and build up of things that you don't necessarily want in your brain while you're sleeping.

You're pruning all those synapses in there. It's just really important for your kind of general brain health and cognitive function, et cetera. These are things that we have evolved over millions and millions of years to work well and to provide a really important function, and we can tap into that with a behavior, which is really cool.

If you want to develop a drug that would change the way your brain prunes, prunes its synapses, where it clears away some of the damage, it's a really challenging undertaking to undertake, right? But we can tap into these really ancient systems that have very potent effects on our biology with a behavior.

So I think that's amazing, right? And so i- it's easy to cast off these things as boring and as simple, and perhaps they are in a sense, but the effect that they can have on us is anything but, and it's a really amazing way that we can [00:15:00] play and modulate with our biology.

Team Science at Sinai

Stephen Calabria: Now, we here at Mount Sinai have made health span a major area of focus, bringing together experts in multiple disciplines: aging, immunity, cardiovascular, neuroscience, imaging, and preventative medicine.

Why is this kind of multidisciplinary approach so important, and what kinds of strides are we looking to realistically make?

Daniel Puleston: I think, aging doesn't respect our departmental boundaries, I think that's one thing. If you wanna hire someone to research the immune system, you- you're gonna hire an immunologist.

If you have a heart attack, you want a cardiologist. But aging, again, is this systemic problem that affects every, every part of us. And so, we need to have this team science because no one scientist's knowledge is deep enough or their expertise wide enough to be able to really glean this deep understanding of some of the mechanisms of aging that happen in our body, that happen between [00:16:00] systems.

So to give you an example of this the immune system, I- I'm biased 'cause I'm an immunologist, is interesting for a number of reasons, but one of the, the things I like to think about the immune system the most is that it's one of the few systems, along with the nervous system and the cardiovascular system, that's present in every tissue.

So we now know that the immune system is not just important for responding to infections. It acts in each tissues to maintain normal operating function of the tissue, right? To keep everything ticking along, everything working well. What we would say the normal homeostasis of the tissue. And this is happening in different ways in each tissue, right?

The immune cells in the liver is interacting with the liver in certain ways to maintain liver homeostasis. But it's hard to have a deep enough knowledge of the liver and then how that's... the immune system is working in the heart to maintain normal heart function, 'cause no one person has all of this knowledge to be able to do this, right?

So this is why it's super important that we have this multidisciplinary approach, that we pull people in from these different areas because there's no way that we can make these discoveries without this, right? Let me give you another example. [00:17:00] In the bone marrow, as we get older, our stem cells accumulate mutations, and these stem cells with mutations, they generate immune cells that go out into our bodies, and they're a bit more inflammatory now that they've acquired these kind of mutations.

And these inflammatory immune cells can go to the heart, and they can go to the walls of aorta, and they can exacerbate cardiovascular disease, and they can also exacerbate cancer development.

So for this discovery to be deciphered in its entirety, you need knowledge of hematology, you need knowledge of immunology, you need knowledge of cardiovascular system.

And so it's not a desire, it's a necessity to have these things. And I think that's what Sinai does really well, is because we have a very collegiate environment, and so there's a lot of cross-fertilization between departments, and so this is a huge advantage that we have, and with that, I think that we do very well here.

Target Aging Upstream

Stephen Calabria: The thing is you're talking about targeting diseases, but at the same time we're wanting to also focus on health span, and one theme emerging from Mount [00:18:00] Sinai's work is the idea of identifying risk earlier before disease becomes apparent.

So what does it mean to target aging to extend lifespan versus just targeting disease?

Daniel Puleston: I think in the past, but back in the day a bit more, there was this kind of conversation. What is the best way to improve health span?

We know what the major drivers of mortality are as we get older: cancer, cardiovascular disease, these kinds of things. Infection, at least it used to be before vaccines.

And so is it a sensible strategy that we should just try and cure these diseases one by one? And if we do this one by one, eventually we're gonna improve health span, and we're gonna put years on our lives.

Or should we target the upstream driver of what many of the diseases derive from, which is aging?

'Cause many of these diseases can be thought of as a disease of aging, because most diseases we develop in later life, right? Cancer we develop later in life, cardiovascular disease, and a lot of it is a consequence of our declining physiology. There

Stephen Calabria: are [00:19:00] aberrations, but-

Daniel Puleston: Yeah ...

Stephen Calabria: yeah.

Daniel Puleston: So it's interesting when you play that out. I think if you were to ask the average person "How many years of life expectancy would you put on the population if you cured cancer tomorrow?" What would you think? So let's say like- I

Stephen Calabria: guess it depends on the cancer,

Daniel Puleston: right? Let, all, all cancers.

Let's imagine you could all cancer tomorrow. Life expectancy now, let's say, is 84, 85. What do you think that would jump to if we cured cancer? Bearing in mind cancer kills about 20% of people in the United States.

Stephen Calabria: I suppose on the one hand, n- 90, but on the other hand, just because you solve for cancer doesn't mean that you solve for all of the other things that make you age.

Daniel Puleston: Getting a good point. You kind of poo-pooed me by giving a really good answer there. Cause I think a lot of people, and I know this because I asked them this, they add 10 years, 15 years, right? 20 years even if we can cure cancer.

But the numbers are super interesting. When you look at this and you model it, you only would add about three years to life expectancy if you cured all cancer tomorrow. And there's a number of different reasons for that, right?

Again, cancer is a disease of old age, so if you're curing someone who's already old, they don't have much longer to live anyway, sadly. [00:20:00] Or, and you cure someone of cancer, but diseases tend to cluster in people, right?

So you might cure them of their cancer, but you haven't cured them of their cardiovascular disease or their diabetes. So this is why the thinking is, let's target the upstream drivers of general poor health and decline in our physiology, which is aging.

So this is the kind of grand concept. We don't know how to do that yet. But this is the kind of thinking. It's, in the long term, a more robust strategy to target upstream aging than cure the individual diseases necessarily.

Of course, we're still trying our really hardest to do these things, right? But if we want big effects on health span, then we have to think about aging in this way.

Longevity Hype and Supplements

Stephen Calabria: There is a lot of hype surrounding longevity right now, some of it not altogether trustworthy. How can patients distinguish between evidence-based health span science, that which you're talking about, and the more dubious, spurious stream of supplements, bio hacks, and [00:21:00] miracle claims circulating online?

Daniel Puleston: Yeah it's so hard, it's even hard for us, people who are trained, i- in many ways. I think where you can is try and take advice from a scientist or a medical professional. It's difficult because not everyone knows a scientist, right?

Someone who doesn't have skin in the game necessarily, who's not trying to sell you something, who just can give you some unbiased, skilled advice.

The zone has been flooded by all these supplements and all this information, and it's so hard to decrypt what's legit and what's not. And some of it is, some of it might be. I'll give you an example and I think a lot of it sounds so reasonable.

So take the case of NAD. NAD is a metabolite. Lots of people take supplements which affect NAD metabolism. The reason being is that it's thought, and there's some evidence for this, that- NED levels as you get older decline S- so therefore it goes that if you can bring those levels back up again, then you're doing something good for aging.

And so there's things you can take, supplements you can take that will in fact, will [00:22:00] indeed bring those NAD levels up again. And okay, this is all sounding very reasonable and very sensible. Something goes down, you take something, it comes back up. Something good must happen when you do that.

But, we just don't know, right?

Just because something shifts from less to more or the other way, and you're doing the opposite of what's happening in aging, doesn't mean that it's gonna give you some healthspan effect or a longevity effect. It's not that it can or that it won't, we just don't know. But of course these people are not massaging this information this way, right?

Stephen Calabria: They're presenting it purely as fact. And I know, and "they" don't.

Daniel Puleston: And these things have been done in mice, and so yeah, okay, there's evidence in mice, and that's legit. And but again, to say that it's gonna do this in a human being, a scientist would be much more cautious about how they would talk about these, these things, whereas the supplement market tends not to be, right?

'Cause they have a bottom line and they're trying to make revenue. And so I think just try and be cognizant of that, that claims are a little bit overblown in the supplement field. And then the other thing I [00:23:00] would say is generally there's no- nothing on the market right now I would say that you should 100% be taking if you're a healthy, normal person with no deficiencies.

There's just, there isn't. Not anything that's backed by robust human, well-powered human clinical studies. Hopefully one day there will be, but there isn't right now. If you're someone who has a deficiency, that's a different matter. That's something you should be thinking about if you're deficient for a vitamin

D or vitamin B, because we know that these deficiencies translate to altered function, right?

Altered immune performance, and when you correct that deficiency, that immune performance comes back. What we do know, which I think is not well understood perhaps by non-scientists in, in the public, is that adding more, topping up doesn't give you more, right? So I think, okay, let's take...

We'll take vitamin C and let's take zinc. And yes, there is evidence, especially for zinc, that, it can play a role in the immune system and people think it can prevent colds and both [00:24:00] zinc and vitamin C. And there's some low level evidence that might be true, and not prevent them, but at least limit the symptoms of

Stephen Calabria: colds.

And therefore, if I add 1,000% of vitamin C per day, that means that I'm never going to get sick from anything.

Daniel Puleston: So, what as an immunologist would address this question would say zinc is important for the function of the immune system because when we take it away, there are deficits in your immune system, right?

And when you correct it, those... You treat those deficits. But if you have normal zinc levels and you have a normal diet and you have no deficiencies Adding all this zinc is not gonna supercharge you, right? It's not gonna make you into- ... He-Man or She-Man, the, the, that new movie that's out with Alison Brie.

So I think this is a misconception that more intake of a thing, of a supplement, vitamin C, vitamin D, is gonna give you all of this super immune power, but it's not the case. And take it from an immunologist you really don't want to be boosting your immune system.

Stephen Calabria: Now, just to be clear to any listeners who are exercising a great [00:25:00] deal of skepticism, you are not on the take from any given entity.

Daniel Puleston: No.

Stephen Calabria: Okay.

Daniel Puleston: I don't take any money from the pharmaceutical supplements.

Stephen Calabria: Okay. Good to know. Yeah. And you specialize in cancer research. Are there aspects of health span research today that remind you of where cancer research or immunology stood a decade or two ago?

Full of promise, but still requiring rigorous science to separate possibility from reality.

Daniel Puleston: Yeah, I think so. I think it, it reminds me a little bit of when I was coming up and I was a student, I was a PhD student, we were right at the beginning of the immunotherapy revolution, right? This idea that you can modulate the immune system to treat disease, particularly cancer. And for the previous decades, this was, it was like a long-held hope of the cancer field and the cancer immunology field that we could do this.

There'd been a lot of attempts, a lot of failures, and when I was coming up, we were really at the cusp of this. We'd learned a bit more about the biology and what might work, and now we have these strategies where we can [00:26:00] modulate the immune system. They're now frontline therapies for cancer and are now saving many people's lives.

And I think it's interesting to think about where we might be for modulation of the immune system for aging, right? Given all the things we talked about, that aging of the immune system is as important just for how you age and your health span. Can we modulate the immune system in a reasonably healthy older person to target aging?

And can we do this in a highly specific way, right? Can we work out that this part of your immune system is not functioning well, but this bit is okay, so can we do something to, to target that? And then I think the other thing that i- is interesting to think about is personalized medicine for aging.

We are moving into this space now where for certain diseases and for cancer, that we have these personalized strategies where we can sequence someone's tumor, understand what mutations are driving their cancer, and develop a vaccine that we can then give to that patient to, to boost the immune response.

And I think that's an interesting thing to think about for aging, right? Can we have a personalized [00:27:00] approach to someone's aging? And one of the things that's really interesting that we've learned very recently, in the last kind

of year or two, is we've learned about kind of markers in the blood which can tell us a little bit about how individual organs are aging.

And what that research has shown us is that not all your organs age at the same rate. You might have an aged brain, but your heart's pretty youthful. So should we be using this information for t- more targeted therapies for aging, right? Do you need to give this big systemic drug or intervention when we can just give something that's gonna just help your brain, right?

Just spruce up your brain a little bit. So I think this is interesting and reminds me a lot about where we are now with immunotherapies and personalized medicine.

Stephen Calabria: Your research also focuses on a fascinating intersection between metabolism, immunity, and cancer. Now, for folks in the audience and folks at this table without a scientific background, what is the [00:28:00] connection between those three areas?

Daniel Puleston: Yeah, I th- I think the cancer metabolism field is a, a bit more established. This idea that cancer cells have a, a certain metabolism and use certain fuels and nutrients to fuel their growth and that this metabolism is maybe a little bit different from the surrounding healthy cells. What was a big advancement in the last 10 to 20 years is this idea that metabolism

And when I say metabolism, I don't mean calorie-

Stephen Calabria: Weight or calories ... weight. It's what your- Yes ... which is what most people ...

Daniel Puleston: Yes. Yes. The, the KFC that you just had. It... the nutrients that individual cells are using, the metabolism that's happening within individual cells. We ... For a long time, immunologists totally ignored metabolism.

It was just something that was happening in the background. Ah, making energy. It's fine. The immune cells need energy. This is fine. I'm sure it's doing something important. But then we had this kind of big breakthrough, which is that the metabolism is actually incredibly vital for the way that the immune system [00:29:00] responds to

And its ability to respond. And so when your immune system is in resting state compared to when it's in an active state, there's huge metabolic changes that

occur, and you can actually change the way that the immune system reacts just by changing the fuels and the nutrients that those immune cells are using.

So you can, for instance, you can kinda dampen down an immune response by preventing the immune cells from getting access to glucose. The other thing that immune cells are really good at is putting on different hats. You might have an immune cell that's in double denim, and then one day it's in a three-piece suit.

It's the same immune cell. It just looks different, acts a little bit different depending on the context, and this kind of, what we would call in science plasticity, but it's just a fancy word for flexibility, this flexibility is important because we need to have this kind of flexibility to respond to different threats in our environment, right?

We have got viruses out there, worms, and bacteria. They require a little bit something different to expel them from the body. So the immune system needs to have flexibility.

And so what we learned is that [00:30:00] metabolism and metabolites endow this kind of flexibility. And you can change, for instance, an immune cell from a very pro-inflammatory state to a very anti-inflammatory state just by playing with what nutrients it has access to.

So if you change its ability to access fat and break down fat, you can totally play with these kind of settings. So this is a big breakthrough, and it's now a field that we call immunometabolism, and this is a big theme in my lab, is how metabolism shapes immune responses.

Stephen Calabria: And within that, you're, it seems, exploring why immune systems become less effective with age. What have you learned about why older adults often have more difficulty fighting infections or responding to vaccines?

Daniel Puleston: Yeah. The immune system really does undergo quite profound remodeling when we get older. One of the main problems that we have is this idea of immunological memory, right?

That when we get infected with something for the first time our body gains a memory to it. And when we see that same bug a second time, we're a bit more adept at responding to it, and [00:31:00] if we're really good, we would even say we were immune.

It doesn't impact us at all a second time around. And what's left behind after that first infection that gives us this memory are cells and antibodies. All right? We would call them memory cells. And they have special qualities, these cells.

They can react faster when you see the bug for a second time, and they can act more potently. So this is what allows you to respond and be immune to these secondary challenges.

As we get older, our ability to form this immune memory becomes a bit perturbed, and it's one of the main reasons why it's really difficult, can be challenging to vaccinate elderly people. Because this memory, which is the basis of long-lasting immunity, that we have these cells and these antibodies circulating within us for many decades, this is what we need to happen for a good vaccine response and to give us long-lasting immunity.

So this is one area which the body becomes less and less effective at, this long-term memory. One of the things that, in my lab actually, with Dr. Miriam Merad, is [00:32:00] we've been working a lot on different parts of the immune system that we see, particularly cells of what we call the innate immune system, these cells called macrophages.

It's a fancy word, but these are cells that eat things. This is how they get their name. These are cells that are really important. They're immune cells, but they sit in all of the tissues, and they're really important for defense. So when you have a bacterial infection, they're really important for eating the bacteria up and digesting them.

But they play really important tissue functions too. So for instance, in the heart, they're important for electrical conductivity of the heart. They're important for clearing all the dead cells away in your body. You generate about 200 billion dead cells every day. They need to be cleared. That's a lot of dead cells.

That's

Stephen Calabria: a lot of dead cells.

Daniel Puleston: Those cells are very efficient at clearing those dead cells away. They're amazing at it. And what others, but also us, have found is that you lose these cells from the tissues. They really start to disappear as you get older.

So we think that leaves you more susceptible to infection, and it makes your tissues functions a little bit less 'cause these cells are so vital for just keeping that [00:33:00] functionality of your organs and your tissues.

And we've been really thinking about ways that we can bring these cells back and improve immune function like this. So these are all some of the things that we've been thinking about.

Stephen Calabria: Cancer risk increases with age. Is that simply because we've lived longer, or are there fundamental changes in the aging immune system that contribute to cancer development?

Daniel Puleston: I think it's both. I think both those things are true. For sure there's a cumulative aspect to cancer. We know that cancer arises in large part because you accumulate these mutations, and these mutations take time to accumulate.

And you need several of these mutations in very particular places of the DNA, things that tend to affect kind of the way the cells divide and the way that cells repair.

So there's this cumulative aspect of acquiring many mutations in the same cell. You reach a kind of tipping point where you go from a cell that's relatively normal, behaving normally to now is changed in some way that puts it on a path [00:34:00] towards being cancerous.

So that's a time-dependent thing, and that's one of the main reasons why you tend to see more cancer in, in, in older adults.

But we know it's not the whole story because interestingly, when you sequence the tissues of people in middle age, you find that actually many people's tissues are full of mutations. Their cells are full of mutations in areas of the genome that we actually would say are...

they're cancer-driving mutations. Exposed skin that's been exposed to sun is full of mutations. Yet in large part, a lot of these people are totally normal, right? You'd... You wouldn't even know this was happening. You wouldn't even know that you know you had these mutations, and you certainly don't have cancer.

So we know it's not the whole story. You can have a mutational burden without having cancer. And so I think this is where the immune system comes in, 'cause one of the things the immune system does is what's called surveillance. So the

immune system constantly is checking your cells to make sure they haven't turned and taken a step on this road to being cancerous.

And when it does, it nips it in the bud [00:35:00] pretty quickly. Kills these kinds of early maybe they could turn into something bad cells, and we call that immune surveillance, and your immune system is very good at this. And we know that if you take away the surveillance, you increase the incidence of cancer.

So of course, we're talking about immune aging here, and we know that the function of the immune system diminishes, so we think that this surveillance program that the immune system carries out is less effective as you get older. One of the reasons may be that this cancer risk increases. And then it comes back to what we were talking about earlier, that your immune system and some of the cells that you need to fight these cancer cells, like your T cells, which do the killing, do the orchestrating, they just don't function so well anymore.

You have diminished functionality in your immune system, and your immune system is really important for keeping that cancer at bay, right? Minimizing its growth rate. So I think it's both. Your immune system plays an important part, and you have this, this cumulative kind of mutational aspect too.

Stephen Calabria: We're closing out the interview. There is something of a conspiracy theory out there that folks are either sitting on the cure for [00:36:00] cancer or that it is just within arm's reach, but society, the medical establishment, what have you, are purposefully obstructing it. Is that true?

Daniel Puleston: No. Total nonsense. That's total nonsense for so many different reasons, right? All right, okay, I work on cancer. If I made a cure for cancer, you can be absolutely sure I'm telling everybody. You can be absolutely sure of it. For so many personal reasons. Forget, like, all the ben- the, the benefits all these patients are gonna have, right?

But you're gonna be selfish. We're scientists, we all have egos. You're g- there's gonna be Nobel Prizes, there's gonna be, there's gonna be money, there's gonna be fame. Your name is gonna be talked about for the next thousand years if you're the person that cured cancer, right? So there's no way that any scientist is keeping that quiet.

And the other thing which is the biggest kind of rational fallacy in this argument is that pharmaceutical companies are somehow less better off for not developing these drugs, [00:37:00] right? Because somehow the drugs that we have the

kind of old drugs, the, the chemotherapeutics, are somehow these big money makers for them.

But they're not, right? Many of them are off patent. It's the new drugs that come through that are the money makers 'cause you have exclusivity for that drug. If you have a cure for cancer, every hospital in the world is going to be buying that drug from you, right? You have this new thing that everybody wants, and you're gonna be able to sell it to them.

Stephen Calabria: So it's not true. The money's not in the cure, as Chris Rock put it. The money's in the medicine.

Daniel Puleston: The two go hand in hand together, no?

The two go hand in hand together. So the the most profitable drugs in, in the world are the new immunotherapeutics. They're new cancer drugs that have come out recently and can, in a subset of patients, do, do amazing things.

So no, from the pharmaceutical company side, from the academic science side, there's no benefit to keeping quiet about this at all.

Stephen Calabria: Sure. Sure. And I imagine also it's not like cancer can be cured by one individual person in a lab somewhere. There has to [00:38:00] be so much cooperation and buy-in from so many different people, and try keeping that quiet.

Future of Healthy Aging

Stephen Calabria: Finally, if there's one message you'd like listeners to take away about healthspan, resilience, and the future of healthy aging, what should they remember the next time they think about their own long-term health?

Daniel Puleston: I think the way we grow biologically and physiologically there's a lot of things that go into shaping our kind of curve through life in terms of our lifespan and our longevity.

Some things we have control over and some things we don't. So your genetics you can't help. For good or for bad, they're gonna shape the way that you respond to disease, your resilience how long you live, what diseases you get, how potent or nasty those diseases are. You really don't have any say over, over this.

And there's a lot of luck involved as you go through life. But there are things which I think we can take comfort in that we can do, right?

We can have some agency and we can have some control over our physiology to some degree by doing all [00:39:00] of these boring things that we've talked about, right? By looking after yourself, by trying to minimize your stress, sleeping well, exercising well, eating well.

Easier said than done, but I think for me, when I think about now I'm moving into the second half of my life and you start to think, "Okay, maybe some of these events are in my future now," and I try and think, "Okay, what is in my control?"

And I think these things are in my control. There's a subset of things that I can do that maybe gives me a, a good chance of maximizing my healthspan and longevity.

Stephen Calabria: Dr. Daniel Puleston, thank you so much for being on Road to Resilience.

Daniel Puleston: Thanks for having me, Stephen.

Stephen Calabria: Thanks again to Dr. Daniel Puleston for his time and expertise. That's all for this episode of Road to Resilience. If you enjoyed it, please rate, review, and subscribe to our podcast on your favorite podcast platform

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Road to Resilience is a production of the Mount Sinai Health System. It's produced by me, Stephen Calabria, and our executive producer, Lucia Lee. From all of us here at Mount Sinai, thanks for listening, and we'll catch you next time, and get that exercise.