Introduction and Cell Danger Response overview

So Dr. Naviaux, oh, thank you so much for joining us on this summit. It is really a great honor to have you here. I have been trying to make this happen for many, many years, and I know that you are generally reluctant to do these kinds of things.

So I really appreciate it. And as I said to you before starting this recording, I think it's a I think it's very important for people to hear from sort of the man himself from from such an influential researcher and thinker in this space.

I can speak for myself and many others, many other experts that I've interviewed on this summit and interviewed over the last five years of doing a podcast that your work, particularly on the Cell Danger Response, has been really a landmark contribution to this field.

And our understanding of certainly chronic fatigue and what's going on in many diseases. So again, thank you for for doing this. So I know you're short on time, so we'll jump straight in.

Can you describe for people who are unfamiliar with it what the cell danger response is and why you believe it's central to understanding chronic fatigue and many other diseases?

Sure. The cell danger responses an evolutionarily conserved universal biologic response to environmental stress, threat, infection or injury. And, you know, it's a normal and reflexive part of life.

We need it to to learn and adapt. We need it, you know, to give gains after exercise. We also need it to fight infections and heal from injuries and to heal from psychological traumas.

So the KDR starts by sensing stress or injury in mitochondria in the cell. And if the threat is slight, like a papercut or scrape or a common cold, the seed is confined to those, in fact those affected tissues.

And if the injury or threat to life is large or infection as severe as with a heart attack or stroke, Lyme disease or a SARS-CoV-2 infection, for example, mitochondria and cells trigger a multi-system and multilayered response that ultimately involves both the brain and body.

So, you know, our research has given us a glimpse of a connection between many chronic illnesses. And when we performed Metabolomic analysis of over a dozen different complex disorders ranging from primary mitochondrial diseases through autism spectrum disorder.

Myalgic Encephalomyelitis and and chronic fatigue syndrome, Gulf War Illness, Depression, Suicidal Ideation, ALS. We found that the pathways that were dysregulated by the so called age response are common to a common denominator in each.

And since we know that genes and environmental risk factors that cause these disorders are actually different in different patients with the same disease, it got us thinking that it's not the specific pathogenic trigger that creates a specific disease.

Instead, it is. Each chronic disorder is caused by a single shared biological response to over hundreds of different pathogenic triggers. And this common biologic response we call the CCR.

What can I ask you? What what are some of those triggers? Well, some of those triggers are, you know, a brilliant infection in Lyme and EBV infection, SARS-CoV-2 infection.

It can be hazardous ball. The volatile organic compounds in you know, in you know, in the workplace you. It can be

a head trauma. It can be.

Pathogenesis vs. salutogenesis

Well, just anything that causes a a stress outside of the normal range of homeostasis ends up triggering, you know, the cell danger response to greater and lesser degrees.

Mm hmm. So, you know, when we started thinking about this, we needed to find a way of integrating, you know, all the the the strong work that has already occurred that uses what we call the pathogenesis paradigm.

And we began to think of causes of disease in two classes, and many different genes. And environmental factors can lead to a disease like autism spectrum disorder or, you know, amyotrophic lateral sclerosis illness that each disease or disorder can be diagnosed by, you know, specific symptoms.

So the causes are different in each patient, but the core symptoms are the same. This led us to think about this concept of penultimate and ultimate causes.

And so the study of penultimate causes of illness is well known. That is the study of pathogenesis. Pathogenesis is the study of different genes and environmental factors that initiate the injury, trigger the KDR and start the entry into the healing cycle.

In contrast, the study of ultimate causes is the study of the shared biologic response that used to exit from the dynamic process that maintains chronic illness.

Now that's the study of solid Genesis. Pathogenesis creates the injury, solid Genesis effects the repair. These are distinct pathways. And it's important to remember that the path to healing cannot be traveled by retracing the path that led to the illness.

Can you elaborate on that, what you mean about that last part, that that the path to healing is not just the simple reversal of the path to illness. Yeah. So so for example, if we develop a pneumococcal pneumonia, we have a bacterial infection of the lung that can be treated with antibiotics, that can eradicate the the bacterium.

But then there's a lot of damage that's done to the, you know, to the lung tissue that has to be repaired and, you know, actually, you know, the removing of of the bacterium is just the first step.

But energy and resources from the body have to be, you know, redirected toward, you know, rebuilding all the broken alveoli and the blood vessels and to reestablish the architecture of the lung. So.

So, yeah. Just knowing. Yeah. Yeah. So that's that's one example. And, you know, we could talk about, you know, head traumas and traumatic head, you know, traumatic brain injuries.

You know, frequently when an injury has occurred, it has a, you know, this long lasting effect that, you know, just knowing what the original cause was, you know, doesn't actually help you to resolve the the final the chronic symptoms.

Mm hmm. So you said the ultimate causes of disease. You described it as things that I'm sort of paraphrasing here, but things that prevent cell you Genesis, things that block the the healing cycle. Yes.

What what's going on there? How would you describe that? Or what kinds of things prevent the body from entering the healing cycle or completing it? Well, sometimes it can be a secondary infection, sometimes.

So sometimes it's helpful to, you know, think of these in the simplest terms. So if you have a cut and it's partially healed, but then, you know, stretch it over overhand and break it open again, the healing process has to go back to the beginning.

It has to start again. It can't just, you know, pick up where you left off. Same thing. If you remove a scab from a scraped knee goes back to the beginning, the same thing happens.

And it's actually been measured in the crashes and chronic fatigue syndrome is that you can, you know, go from one state of metabolism to a state that's more dependent on glycolysis and more inflammatory.

That's, you know, after a crash that then requires you to make make your way back to your baseline after that after the crash.

Why healing gets blocked

So so I guess the you know, the important thing to remember is, is that reentry can, you know, keep you in the healing cycle. But sometimes what happens is the the you, you know, the the cells that initiated the the signals of of danger and threat that triggered the initial cell danger response.

And the brain that is responding to sensory information sent from the cells haven't yet been convinced that the the world is safe enough to heal yet. And so, you know, it keeps the the signals going that maintain defense even even when the, you know, the actual triggers are, in fact, gone.

I know. I sent you a list of questions I wanted to ask you for this this interview prior to it. I want to jump a little bit ahead, because I feel it's a natural segway with where we are, where where we're at in this conversation.

So just going further on, Sally Genesis, do you feel that this concept that you're describing as far as the healing cycle has been incorporated or properly incorporated into the the conventional medical paradigm, the Western medical paradigm?

Not at all. In fact, you know, our training in the scientific method and in Western medicine has really focused on the things that have been successful up to now, which is, you know, in in in Western thinking, typically isolate a single variable in doing your experiments.

And, you know, listen with your experiments, ask a question of nature and then listen to the results and design a new experiment that's very effective when a disease or process is regulated by single things.

But what we find in in the vast majority of chronic illness is that they're plural causal. That means, you know, that's a term that was used by hun cilia.

That basically means that, you know, for example, you can you can take, you know, a disorder like LSD and you can have an ascending mutation that can lead to it.

You can have a TDP 43 mutation that could lead to it. Now they almost never happen in the same patient. They're these are just different things, different ways to get to the same, you know, the same problem.

And so ultimately, you know, so so we've we've been taught to think about diseases in a in a in a way that has been effective in the past but is not very effective.

It at understanding dynamical processes. Okay. So then and you know, a lot of our inspiration comes from the fields of ecology and evolutionary biology.

And so that led to us thinking about solid Genesis as a dynamic process that has regulate, you know, regulators that can, you know, drive outcomes in one direction or another, but or or not on and off switches.

Okay. And so so you know what? I think a solid genesis as a multilayered process that starts with mitochondria and cellular changes that ultimately can grow to change whole body behavior and metabolism and the autonomic and endocrine systems and the microbiome are always engaged, you know, when the KDR is activated.

But because solid Genesis, you know, healing is energy and resource consuming, you have to actually take materials to heal a broken bone or to recover from a heart attack, for example, that, you know, you can't restore, you know, full and vibrant health without being able to redirect those energy and resources away from self defense and back to normal cellular functions.

Mm hmm. So I guess, yeah.

Western medicine and the need for a new paradigm

So that kind of leads to this natural idea that, you know, we talk about pathogenesis based approaches to medicine that's filling the, you know, this book that has been you know, we've been writing for the past 5000 years of written history that I call the first book of medicine that really is based on the pathogenesis paradigm and has been very, very effective or, you know, many acute disorders.

But I believe that to discover effective treatments for chronic illness, we need a new paradigm and a new way to do medical research for discovery. And I think that that, you know, study of social justice based treatments and the process of the molecular process of healing, we hope.

Right. The pages of the second book of Medicine. Can I offer an example? Disease and maybe see how you might think about it differently. And you can feel free to suggest a different one if this one doesn't resonate with you.

Let's take heart disease and sort of atherosclerotic heart disease as an example. Again, feel free to change the model if you'd like. And the way that the conventional medical paradigm thinks about this in an oversimplified way is essentially that there are there are factors in the bloodstream, things off with cholesterol and LDL and oxidized LDL and lipoprotein a lipoprotein B and ultimately, these these factors are driving this atherosclerotic process.

There's there's factors that are causing endothelial injury to the blood vessel lining. And then you get these LDL oxidizes, LDL particles, particles incorporating into the blood vessel wall driving this disease process.

And the typical sort of thinking about this and that and the standard medical model would be to apply statin drugs. So sort of operating in this pathogen SS model and then applying a drug intervention to, to interrupt or slow down the development of that atherosclerotic plaque.

And how might you from the second book of medicine, how might you think about this differently or what layers would you add? And again, feel free to change the disease model if it suits you.

I can I can work with this. I mean, one of the things that distinguishes coronary artery disease from a lot of the other disorders that that, you know, we've studied is that there is objective of histo pathological structural change.

And so so, you know, a lot of disorders are due to just functional changes in how the cell responds to signaling and don't have to, you know, lead to structural disorders.

But in in that case, you know, what we know is, is that stress leads to inflammation, leads to oxidized cholesterol, lipoprotein particle in lipoprotein particles.

And even, you know, when studies were done on 20 year olds that had, you know, been in in the stress of battle in Vietnam, coronary artery disease was rampant.

And, you know, young men. And so, you know, the process of preventing coronary artery disease is you know, it is something that I think will have, you know, we have to address as well the process of remodeling coronary arteries after, you know, let's say, you know, we have, you know, foamy macrophage changes, you know, and growth of underlying smooth muscle cells.

It takes a more concerted effort that is still going to start with, you know, being able to to provide those cells that are currently working under signals that trigger the, you know, the inflammatory or the first phase of the cell danger

response that the the danger has gone.

Now, you won't be very successful at doing that if, in fact, the people are still fighting a war or, you know, they they are otherwise engaged in activities that produce a systemic stress response that is chronic.

So, you know, ultimately. Yeah, well, so I don't want to get too far down this line because I know I mean, so so far the only way to so we can we can decrease the rate of, you know, of progression in atherosclerotic coronary artery disease with statins.

But we can't reverse it. No, no.

Coronary artery disease as an example

Study has shown that statins reverse coronary artery disease. However you know, there can be slow reversal with methods that, you know, combine a very dramatic change in in diet with exercise and, you know, plus minus statements that can then result in something, you know, measured angiographic improvements of, you know, up to 7% in a year, let's say they're still modest, but they're the only time.

They're the only that combination therapy has been the only thing that's been shown to actually reverse the the stenosis in coronary artery disease. Coming from a big picture, sort of a 30,000 foot view meta level of all of this.

And looking at the Western medical paradigm, as you know, as you said, not really incorporating this concept of cell you genesis and more operating from the frame of trying to look at every individual disease and do research to uncover the specific meq and physiological mechanisms, biochemical pathways that are abnormal or pathological that are then framed as driving the disease process.

So if you have depression, then you know it's because of a serotonin deficiency in your brain. And if you have atherosclerosis, it's because you've got this too much oxidized LDL entering the blood vessel wall and if you've got high blood pressure, then we're going to use a drug that interrupts the way your kidney regulates water and electrolytes or relaxes the blood vessel walls to sort of interrupt what the body is doing to change it, how how might we start, you know, again, from a metal level without getting too specific on the diseases?

How might we think differently if we're incorporating the concept of cell you Genesis and maybe having more respect for sort of this innate capacity of the body to heal itself?

Well, a lot of we think of this as you know, a lot of this requires getting out of the way of this natural process of healing k releasing the blocks and and then taking advantage of some of the persistent danger signaling pathways that we can regulate.

And one or one of those ends up being the you know, one of the most ancient danger signals is the release of extracellular ATP. And it turns out that once the ATP inside the cell is a good thing.

It's an energy carrier. ATP outside the cell is a damage associated molecular pattern that that actually binds to, you know, over a dozen different what are called pure magick receptors and no.

And sends the signal of danger. And so what we have found in an experimental work is that we can send the signal of safety by using drugs that actually compete with extracellular or ATP.

And gradually the system begins to write itself. And we have a small clinical trial in autism where we used a drug to to compete with that extracellular ATP.

And the results were dramatic. We had children that spoke the first sentences of their life and still had dramatic improvements in school performance and and many other aspects of their life that that helped them to be more social with it and with family members and, you know, begin to to kind of break out from behind the veil that holds back a lot of children with autism.

So so anyway, this is a without getting, you know, too far along on that. You know, we think that, you know, that there are some very ancient signals that can get stuck and that we can help by removing those signals.

But this is going to be a multi it's going to take a multi-pronged approach. It's not going to be one thing that is going to solve chronic illness. But, you know, I think that unless we begin to look at a different doctor now.

You cut out there at the end, I don't know if. Is your sound still there? Yeah, I can hear you. Okay. So I just.

Safety signaling and therapeutic approaches

Yeah, at the end I just said that, you know, unless, you know, we we begin to to, you know, study the problem, you know, with with a different lens. We're not going to be able to to find the solutions that we need.

With that in mind, I know one of the things that we share is the importance of seeing health, human health through an evolutionary lens and the importance of evolutionary biology in looking at human health and disease.

Can can you talk about why you feel that's important? No. So a a scientist named Theodosius Tobolowsky once famously said that nothing in biology makes sense except in the light of evolution.

And we are all you know, we are all just biological beings that have received our genes from our ancestors. Another quote that helps me understand why the body places such a high premium on defense and healing is one by John Dryden, who once said Self-defense is nature's oldest law so no organism can survive unless it can defend itself from danger.

And and I combine these ideas in an observation that can be put together in a sentence that without healing, multicellular life on earth would not exist.

And without healing, one injury predisposes to another, leading to disability, chronic disease, accelerated and aging and death. So so we are, you know, we're all descended from ancestors who survived each infection, plague, famine, war and other injuries until the at least the birth of their first child.

Now, that's our inherited genetic legacy that we're born with. And so the problem that we have now is the world is changing and those genes are not enough.

We are encountering factors that were never encountered by our ancestors. And these new factors press our DNA to its limits. This mismatch between the current environment and our genes is an equal genetic mismatch that leads to disease and the susceptibility to chronic illness.

So know we can't change our genes, but we can change environmental factors and behaviors that could lead to disease and that can be preventing recovery.

So, you know, our metabolism or our chemistry measured in the blood is know you could imagine a drop of blood as containing the chemical. Conversely, of all the human cells and all the bacterial cells in our body and that real time, you know, chemistry is the real time interaction of our genes and the environment.

And so that's why our work in metabolomics has been such a powerful tool to help us understand hidden connections between diseases. I know that we we have to to wrap up here.

I want to ask you, based on this model, which you've been developing for over a decade now, and all the insights you've gleaned from metabolomics research into these various diseases and how the cell danger response operates and how the cell eugenicist mechanisms operate and what sort of keeps them stuck.

What insights would you share with people sort of on a on a practical level, if you want to go there or how would you want to re-envision how medical research is done to, to, to treat diseases?

What insights can you offer people to get? Well, how should we be thinking about getting well from these different chronic disease states based on the insights from your model?

So, you know, this this model does not overturn the pathogenesis model. It just adds to it and know. So on the one hand, you know, master clinicians, you know, already have in mind, you know, a framework for for treating chronic illness that involves removing the trigger support the weak points for example cast a broken leg, support the heat healing process and remove any factors or infections that would that impede healing.

And then once the initial, you know, healing is complete and the cast is off, then gradually reintroduce the cardinal elements of health and safety to consolidate that message of safety in that to to shift body metabolism away from defense and toward, you know, toward recovery.

And so, you know, I mean, we so we already know and people have used the basics of good nutrition, restorative sleep, wakeful activity, toxin removal, nature, connection, pro-social behaviors.

But we have precious few other arrows in the medical quiver for chronic illness.

Evolutionary biology and practical implications

And that's because I think that most of the current arrows were designed to hit different targets. And so, you know, I'm I believe that, you know, things like any pure energy therapy connects and channel blockers, you know, a variety of devices, including transcranial magnetic stimulation, transcranial bio modulation, mindfulness meditation.

You know, a variety of behavioral interventions will all, all be synergistic. And and I think, you know, we just need good clinical trials to be able to to test, you know, new treatments and devices alone and in combination because unless something is proven in, you know, a in a well-designed randomized clinical trial, it will not become won't be it won't become a new foundation for medical education.

It won't be, you know, become part of the academic, medical, you know, base of knowledge from which, you know, new treatments, you know, can can be born.

So so, you know, yeah. So I so I'm very enthusiastic about a number of new therapies that are designed to get at the, the, the, you know, the dynamics of the healing process and to remove the blocks.

But there will be many other people, you know, more clever than me that will come up with new ways to unblock the healing process and to restore our, you know, vibrant health.

I have one last question for you. One of my personal curiosities, one of my big areas of interest is were medic stress. And I noticed that was not on your list of, as you describe them, the arrows in the medical quiver and I'm wondering, you know, as you're in your model, you have this kind of model of getting stuck in the cell danger response, getting stuck in, you know, something's blocking the healing cycle.

And this sort of state of chronic danger signaling is getting preserved. Do you see a role for perturbations of that system via who are medic stressors like, let's say, physical activity, but heat, cold fasting, breath holding practices, things of that nature in creating slight percher basins where you sort of push the system a bit further, very counterintuitively, instead of removing the stress load, you're pushing the system acutely, transiently slightly further into the state of stress where it might be able to better sense that it's out of balance and return itself to a proper healing cycle.

Does that make sense to you or not? Well, yes, we just have to be careful in, you know, in in selecting the particular stresses that can you know, that would not be damaging to a person in their particular, you know, a particular situation and the stage at which they're, you know, their disease is.

But, you know, the you need the KDR for me. So as it is, you know, it is necessary to create the metabolic memories that, you know, stay with the body and cells after you've recovered.

So so it's it's critical and it's, you know, it's possible that selecting the right or medic challenges could be a part of of this this this approach to unblocking the healing response and to to allow more cells to get back to vibrant health.

Dr. Nabeel, thank you so much for doing this. Are there any final words that you want to leave people with? Yeah, I'll I'll just say that I believe that solid Genesis based therapies will begin where pathogenesis based therapies and I really hope that will be, you know, many, many physicians and health care workers and medical students around the world that, you know, begin thinking deeply about the process of healing.

All right. Thank you so much, your time. I really appreciate it. Okay, thanks. Bye bye.