Sue Nelson
Hello, I'm Sue Nelson and welcome to the Create the Future podcast, brought to you by the Queen Elizabeth Prize for Engineering. Celebrating engineering visionaries and inspiring creative minds.
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Today's guest Khalil Ramadi was named an under 35 MIT Tech Review Innovator in 2020, and is an advocate of neuromodulation therapies, which stimulate the brain's neural circuits to treat diseases such as Parkinson's. But the type of therapies he works on offer less invasive methods than surgically inserting an electronic chip implant in the brain, for instance, and can involve simply swallowing a pill, or, as he's put it, "hacking the brain through the stomach". Khalil is Assistant Professor of Bioengineering and director of the Laboratory for Advanced Neuroengineering, and Translational Medicine at NYU Abu Dhabi. And he speaks Arabic, Spanish, and thankfully for me, English as well. Khalil, welcome to the podcast.

Khalil Ramadi
Thank you so much Sue, it's really a pleasure to be here. Thank you for having me.

Sue Nelson
Now, I mentioned neuromodulation therapies, gave one example with a chip for Parkinson's. What are the other diseases and areas that neuromodulation therapies can actually help within the body?

Khalil Ramadi
There really are a wide variety of diseases where the nervous system comes into play. And so I can share a little bit about where the current thinking on this field is, but I should make the note that it really is an evolving field of research. And there are increasingly more diseases that we originally, you know, did not connect with the nervous system, that we are indeed finding have some sort of neural dysfunction component to them. But at least you know, as it relates to some of our work, we're really primarily interested on the diseases that arise from some sort of neural dysfunction in the gastrointestinal tract, or in the gut. And as you might imagine, you know, the gut is one of the primary ways that we that we interface with the world, you know, if we don't eat for a while, we get hangry. You know, good conversations always happen over good food. And so it really has this central effect, which I think goes to speak to how interconnected the gut and the brain are. So other diseases that we might tackle with neuromodulation, at least as it relates to the gut, are digestive diseases, anything that you know, changes metabolism, for example, diabetes, obesity, in the case of regulating how we can control hunger, how we digest food, there's also a whole basket of immunologic diseases, or autoimmune diseases that are now recognized to take part, or at least in part, start off in the colon or in the large intestine. And so you can even do some sort of immune modulation through the nervous system in the colon as well. They are just a bit of a taste on what were the current understanding is.

Sue Nelson
Briefly, how do these therapies work? Let's start with the ones that perhaps people are more familiar with, a chip implant, how do they actually work?

Khalil Ramadi
Neuromodulation therapies essentially try to leverage the fact that the language through which the nervous system communicates is essentially electricity, you know, the electricity that we plug in our computers and the phones to charge to, that is controlled by the flow of electrons. In the body, what we have is a flow of ions. And so these ions basically create electrical signals or circuits. And that's how we have information relayed from one part of the body through neurons in a quick and efficient manner. So, when we come to neuromodulation, you know, technically there are multiple different ways you might modulate neurons, which is really what we're saying. One of the most popular ways, even historically, if you look back has been through the use of electricity.

And so predominantly, that has involved placing some sort of conducting material for instance, an electrode, and then applying some sort of electrical current or voltage through it. To your point about other sort of electronic chips. I mean, there are a number of different reasons why we might do that some chips act more as sensors were the primary goal is to gather data, while others might actually involve the delivery of certain kinds of stimuli. And so electricity is one example of such stimuli.

Sue Nelson
So, it's looking at a body as an electronic circuit effectively, which then makes sort of an engineering mind such a sort of good way to approach potential therapies?

Khalil Ramadi
Absolutely. I think that's a great metaphor. And there's actually, I just ordered a book yesterday in the mail, no affiliation, but there's a recent book about, you know, electricity in the body and how our understanding of it has evolved over the ages. I think there's a little fun fact that, you know, electric eels or electric rays were used as early as in the time of the Greeks. And I think there's at least a anecdotal story that Aristotle would try to use these electric eels to zap people who were in chronic pain, which indeed is, you know, one kind of therapy that we have for chronic pain is very selective stimulation of certain nerve bundles. So, you know, it goes way back, we were kind of reimagining it, I think this, this approach of like you mentioned, applying an engineering mindset and developing new kinds of tools is really where the novelty comes in, that engineering advances have enabled us to do things like put all these electronics on a chip, rather than walk around with, you know, giant aquariums of electric fields.

Sue Nelson
That's amazing to realize how far back that goes. Because when I was doing some research for this, you know, you mentioned how it was an evolving field. And I was interested to discover that this is a pretty recent field with the first implant for pain relief being performed in the late 1960s. So as this is, Aristotle aside, a pretty recent field of medicine and bioengineering, why do you think the current methods need upgrading, essentially?

Khalil Ramadi
This is a fundamental balance, we always strive to when developing new therapies of how much do you need to understand how these therapies work, so long as they improve patient's health. And so with that sort of mindset, I think a lot of the early clinical efforts, you know, the, the one maybe that is most well, one that's very obvious that comes up is, for example, electroshock therapy that was depicted in the movie, One Flew Over the Cuckoo's Nest with...

Sue Nelson
Jack Nicholson.

Khalil Ramadi
Of course. That was a approach for treating psychiatric conditions. And, you know, despite sort of the crude nature of the actual therapy, and obviously dramatized a little bit in that movie, you know, it did help some patients, and it still is a therapy that we use today. But if you were to ask the scientific question on, why does it work, that you will find them a number of different reasons, and you'll be surprised how many therapies we still have for neuromodulation that we use even day in and day out in the clinic, and still don't have a fundamental understanding of why they work. In the last 20 years, we've had this other huge jump in into the neuroscience field with the advent of things like optogenetics, or other technologies that allow us to basically, really understand how all these different types of neurons in the body and how they're connected. And so luckily for

us, given that we are primarily interested in neuromodulation, that understanding goes hand in hand with being able to develop tools more tailored to the specific actions we're trying to achieve.

Sue Nelson
And it's interesting how, you know, you mentioned optogenetics, which is using light, and one area that you're specifically interested in is, is sort of getting to the brain via the stomach. And you've often called call this sort of a bio nudge that look like a pill, which, and it does, it just looks like a sort of headache tablet, and you call them ingestible electronics, so what's inside that really small pill?

Khalil Ramadi
Just like the pills that we take today are basically loaded with different kinds of medicines or drugs. So, these pills essentially acts instead of delivering chemical stimuli or substances, they deliver electrical stimuli going back to, you know, what the essence of neuromodulation is, we use electricity as a means of zapping specific cells along the gut to achieve some sort of outcome. And so these pills basically carry different types of electronic circuitry on the inside that is not exposed to the body, but rather the part that really connects with the body or these electrodes that we have on the outside. And so that's through which these electrical signals pass, I should note that unlike, you know, pills that we take, where you actually have some substance that is entering the body and exiting it, there is no such thing. So in this case, you basically have an electrical signal or potential, so voltage or current that goes into tissue, and you're not actually delivering or depositing any sort of metal or electrodes or electronics in the body permanently.

Sue Nelson
So are you sort of effectively doing micro electric shocks from the inside of the body instead of what used to be done in massive voltages on the outside of someone's brain?

Khalil Ramadi
100% correct, yes. I think the other thing that I will add there, though, is that the reason why we are so interested in the GI tract specifically, is because if you think about what we call inside or outside the body, by many measures, the GI tract is even though it runs through us is in fact, considering the inside of our body, considered not part of the body, right, we have bacteria that live there, but we don't get infected, we eat all sorts of things that aren't sterile. And so as a result, you know, mouth to rectum, and basically is kind of this sweet spot of being able to access inner points in our body, while at the same time still not having to have some of the considerations that we do when we implant things under the skin even right, given that we don't want, you want things to stay clean or not infected. And so that's just one little tidbit that I want to note that is a bit unintuitive, about what we call inside or outside the body.

Sue Nelson
It must also be a very delicate balance, because we know that the stomach acid, you also know that if you take a normal sort of headache pill, the pill is designed to dissolve in a certain way in order to deliver the chemicals at you know the right point and the right amount. If you've got miniature electronics in there, how do you protect the electronics from the stomach acid, while still actually allowing it to deliver small bursts of electricity as and when you need it?

Khalil Ramadi
Yeah, that's a great question. And I think this is, you hit the nail on the head, that is one of the difficulties with targeting the stomach and the GI tract. And I'll even go one step further and say that yes, for example, in the stomach, you have the considerations of acid. But then if you continue down the GI tract, what you basically have is a series of segments, each with its own challenges that are very distinct. And so while you can design

from an engineering standpoint, systems that are mechanically robust enough and chemically robust enough to, for example, avoid degradation or avoid breaking down, that challenge is compounded by the fact that you need to do that for multiple different segments as well. And so there it becomes a question of basically asking how we might design devices that can be ingested in a collapsed state, have them sort of unfold to do whatever they need to do and that unfold can be literal or just in terms of a mechanism and then be able to again, go back to being collapsed and to be able to be excreted safely, but that's a major challenge that we have.

Sue Nelson
I'm on what stage are you at with these devices?

Khalil Ramadi
Our work is definitely ongoing. I think we have prototypes that we have put in preclinical testing. I've been going quite well. And then I think, you know, towards maybe this is a bit anticipating a question you might ask later, but getting towards ultimate wider scale deployment or access to these, I think we also need to grapple with questions on, you know, how long do they stay in, in the GI tract? How long can they perform their function? And do we really want to be excreting one electronic pill a day? How are we going to retrieve these? Are these going to go down the toilet and be flushed? It's probably not a great idea. So, there are other questions there that I think beyond showing the use case, which I think is where some of our work has focused now and has been quite positive. I think the following steps need to take these practical considerations into mind as well.

Sue Nelson
Now, you mentioned about your being an engineer your degrees in mechanical engineering and bioengineering from Pennsylvania State University. You have a master's in mechanical engineering at MIT, what made you lean towards bioengineering as a career and the area of medicine?

Khalil Ramadi
I joke that if you if you talk to high school me, I actually really wanted to work on planes. I loved aerospace. And as luck would have it, you know, I talked to a few people, some of my mentors, and they're saying, well, you know, Space X wasn't Space X wasn't around at the time. And so they said, Well, if you go down to aerospace, you're basically going to work for Airbus or Boeing. And so they said, Why don't you stay a little bit more broad do mechanical instead. And so I did that. And then, you know, a few years into mechanical, I think I kind of realized I missed biology. I think this is something that occurred to me as I went in and out of clinics just for check-ups. And I think it's a bit of a humbling experience to whenever you go into a hospital and something that I really wanted to be a part of. So that led me towards the bioengineering route, specifically with a focus on trying to design technologies to have an impact on patient care and human health, but still applying sort of the mechanical engineering toolkit of building physical devices to perform different functions.

Sue Nelson
And It's interesting that often, when I've spoken to bioengineers, that desire, that sort of human condition, the human body that the desire to help, it's definitely you know, a common theme amongst engineers in this area, that they really do see a sort of ethical point to their work, although to be fair, you know, most engineering has a sort of, you know, problem solving based aspect of it that that is also there in helping people. In terms of your other air areas of research is because it's so connected if you're looking at these ingestible electronics that you could then deliver drugs in maybe a new way, with something called neural drug delivery?

Khalil Ramadi

Yeah. So I try to base projects in our lab on fundamental clinical needs. And so, when we, you know, speaking on the ingestible pill front, they are, you're right, engineers like to think in terms of problem statements. The problem statement is that, you know, medicines have a lot of side effects. And surgeries are invasive, and, you know, have recovery times and other off target effects as well. And so, the question there is, can we do things that are more targeted and less invasive than either of those. For the neural drug delivery space. I mean, that's an issue that also is kind of rooted in the problem of when you take drugs orally, they go everywhere. And so, for example, in Parkinson's disease, what you find is a lot of the medication that we that we take, or that we have for these patients are meant to supplement basically a deficiency in dopamine levels in a specific part of the brain. One of the main issues we face as patients get progressively more depleted in terms of dopamine in the circuit, is that the actual basically pro dopaminergic drugs that we take orally, you know, we have a pretty good mechanism of having them only be up taken by the brain. But then within the brain, you start having basically too much dopamine uptake in regions that are perfectly healthy. And so again, you go back to this dopamine dysfunction. And so that's the sort of, you know, case study, I think that we are focused on asking the question of, can we deliver these drugs in a more targeted, more efficient manner. Now, there what we've worked on have been basically developing probes or little tiny cannula or tubes, that we can implant into the brain and leave chronically implanted. And you know, we do a variety of engineering trickery to try to make these as small as possible, as flexible as possible, really, with the goal of avoiding off these all these off-target effects as well. And so that's that same approach can be translated over to other conditions, like epilepsy, for example, where again, you have this, this issue where the drugs we have we take orally, they go everywhere, and they kind of don't enable a patient to fully sort of regain a quality of life without significant off-target effects.

Sue Nelson
Let's go into that engineering trickery that you mentioned, in terms of the probes for the brain, what do you actually do to improve them?

Khalil Ramadi
The goal with anything in the brain is basically to one make it as small as possible. And to make it as inert as possible to avoid any sort of long-term inflammation or reaction from the body. There are, I guess, I'll throw in a caveat that we do have some research and others are also working on trying to make these implants more living, more made of basically biological materials that would really integrate. But that is, I think, a little bit still upstream in the experimental side. But as far as these probes go, you know, you have a couple of different issues. So if you look back, for example, at some of the Deep Brain Stimulation systems from the 1970s, which were the first generation of them, these probes were, they tend to be roughly the size of a chopstick, right, so on the order of a couple of millimetres, and the reason that they are that relatively big is that one, they need to be pretty rigid in terms of being able to be implanted. And they also need to be rigid in terms of being able to know where they are going for, you know, in terms of trajectory. So for example, the way that these probes are implanted in the brain is you basically have xyz coordinates where you navigate to, and then you go in a little bit blind to a certain extent that you're not really, you know, opening and exposing the whole brain, you're kind of just relying on them to go in in a certain way. And so, one of the issues that we faced was that as you make these probes smaller and smaller, now we're getting away from a chopstick size and we're ending up more speaking on something like a hair, right, so you take an individual strand of hair, and try to poke that hair into say some yogurt or jello, 99.9% of the time, it will not go in in a straight trajectory, it's gonna go in all sorts of flimsy because it's not a mechanically robust structure. And so some of the engineering approaches that we've taken there have basically said, how can we make these probes smaller to make them less invasive, less reactive, less dramatic during insertion, while at the same time retaining their placement, for example. And so there, we have some work, showing that just even applying a mechanical polish to this to this probe, but the tip

can actually guide this probe in different ways. And so by rotating it, for example, on the way in, you can kind of basically guide in three dimensions where this little hair ends up.

Sue Nelson
Funnily enough, that was one of my first thoughts would be that sharpen the tip. Sometimes, isn't it, it feels as if it takes a fresh, simple approach to something to get to the heart of it.

Khalil Ramadi
And I think most engineering approaches in medicine that are successful that I have seen, employ that exact mentality, right, trying to really break down a problem and not over engineer or apply too much technology to it, but rather go the opposite direction and say, what is the minimum amount of technology that I need to incorporate to achieve a certain goal? You're absolutely correct.

Sue Nelson
So where did your love of engineering come from? Has it always been there? Or was it something from university onwards? Was there a sort of an event in your childhood that just made you think I just love finding out how things work, fixing things?

Khalil Ramadi
That's a great question. I don't think it was so much how things work, I think it was looking at how things were designed. And this is something that I think has evolved. But I you know, what, what fascinate me in a certain way, are problems. And I don't mean problems like big scale problems. I mean, just even looking at how individuals interact with technology, I think are really fascinating, because I think everyone walking around the street has problems that they have come up with their own solutions for. And I don't think we do enough to acknowledge that. And this is, I think, something that we could do better for the younger generation to show them that engineering is not necessarily all applying physics and math and complicated equations, but rather just the way to problem solve. I think responsible engineering needs to be done, taking into account all the different stakeholders that may be affected by it. Nowhere is that more important than medicine, where I think that, really the role of engineers is, you know, has the potential to be this joining factor between the technical world, the clinical world and the patient's world as well.

Sue Nelson
And did you really find that when you were interning at a hospital as part of your PhD because I saw that you, I love this expression, that you'd written in a blog, you called yourself an engineer in a white coat?

Khalil Ramadi
Yeah, that was, I don't want to call an identity crisis. But I definitely felt like I had split personalities. No, so I, you know, I'm really grateful I think for experiences, such as those that I had during my PhD because, you know, there you are basically immersed in the clinical world. And you get really a first-hand view of what happens when you try to incorporate new technologies in the clinic. And you see that sometimes, really the reason why new technologies or techniques might fail are not because they're not good or not because they don't work but because they just don't fit into a specific culture in the clinic or hospital or because you are, you know, assuming that certain people will do things when they don't need to, like, you know, for example, like if you try to add any sort of technology saying, you know, we can actually reduce the presence of disease or side effect X, were patient in the hospital, nurses just have to do this one thing, or only take one minute per patient, forget it, that's not going to happen, right. And it's especially not going to happen if you approach this without actually consulting with the nurses first. So again, it comes back to these technologies don't exist in a vacuum, they

have to fit into a culture that already exists. And so, engaging with the people that are part of that culture, I think, is a crucial component in what we do as engineers.

Sue Nelson
And engineering is all about technology and innovation and seeing connections. And there have been some amazing innovations that have been awarded the Queen Elizabeth Prize for Engineering. I mean, this is a really interesting area as well. But it's Is there a sort of a type of engineering that you would like to see win the prize one day?

Khalil Ramadi
I'm not sure, I mean, I'll be biased and say that I think the kind of work that we do in terms of neuromodulation less invasively is really cool. What I really enjoyed honestly, seeing the recent winners of the Queen Elizabeth Engineering Prize has been seeing that all these technologies have really impacted patients. And I think this is something that, again, the engineering world is sometimes not blind to but sort of focuses more on the development of technologies that are cool or sexy, rather than focusing on which ones have actually gone on to impact patients. I'll have to get back to you on a specific one.

Sue Nelson
Khalil Ramadi. Thank you very much for joining me on the Create the Future podcast.

Khalil Ramadi
Thank you very much Sue, I really really enjoyed our chat.

Sue Nelson
Me too. Find out more about the Queen Elizabeth Prize for Engineering by following @qeprize on Twitter and Instagram or visit qeprize.org. Thanks for listening and join me again next time.