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

[00:00:10] On this episode, we welcome Brian Brown, PhD, an immunologist and molecular biologist at the Icahn School of Medicine at Mount Sinai. Dr. Brown is the Vice Chair and the Director of the Genomics Institute of the Icahn School, and the associate director of the school's Precision Immunology Institute.

[00:00:28] On today's program, Dr. Brown discusses the growing role of genetics in treating major diseases like cancer, and the resilience that scientists must often show in the face of dismissal of their ideas or outright opposition to their findings. We're honored to have Dr. Brown on the show.

[00:00:45] Dr. Brian Brown, welcome to Road to Resilience.

[00:00:48] **Brian Brown:** Thank you. Thank you for having me.

[00:00:50] **Stephen Calabria:** Can you provide an overview of your background and experience?

[00:00:54] **Brian Brown:** Yeah, so I am a scientist. I trained in Canada. My scientific training is in gene therapy and immunology. I did my part of my training in Milan, Italy, with one of the kind of the foremost groups of gene therapy in the world.

[00:01:10] And then in 2007, I was recruited to Mount Sinai to the Department of Genetics and Genomic Sciences, started my lab here. And, quickly started working on a number of different things, including sort of work at the intersection of immunology and gene therapy, and then moved towards a lot of cancer focused research.

[00:01:31] And, , in 2016, I became the associate director of the Immunology Institute, and then two years ago, I became the director of the ICON Genomics Institute, and my lab is kind of now spread into work that is both looking for cancer immunotherapy targets and also developing new immunotherapies using genetic engineering of cells as well as mRNA and lipid nanoparticle type vaccine approaches.

[00:01:57] **Stephen Calabria:** Was genetics always your area of focus?

[00:02:00] **Brian Brown:** So I'm not a geneticist. I'm really a molecular biologist, a biotechnologist and an immunologist. So I really, more than genetics, I like to play with genes and use them to perform genetic engineering. And this has been sort of my focus with the idea that you can really.

[00:02:19] Starting more than 20 years ago, I just was taken by the idea that the genome is really, you know, the fundamental blueprints of life, and if we can sort of engineer it in a particular way, in the same way that we can use engineering to get a car to drive us across the country or a plane to fly us from one continent to the other we can use engineering of genes to treat and cure disease and that that concept really took me and and has been the basis of my work for more than 20 years.

[00:02:52] My initial foray into biomedicine and medicine was really as an EMT I was an ambulance attendant in Canada and you know, when you do that work, you come across the sickest patients. Most of the people that we interact with are probably in their last two or three years of their life.

[00:03:10] And, as an ambulance attendant, you don't treat patients longterm. You deal with them for at most an hour. And so we would see patients, we'd bring them into the hospital.

[00:03:21] And one day I had been speaking to the one of the physicians that I had gotten to know and asked about how a particular patient did and they said to me, you know, that we had brought in for, they were in cardiac arrest and essentially the physician told me they didn't make it and they never do.

[00:03:39] It's very rare and it was sort of hit me at that time. I was quite young at the time. And, you know, you think about you're there to save lives and you try your best. But you realize, thinking about it more, can we really save someone at the very end of their life? You know, what do we, we really need to treat them much, much earlier.

[00:03:58] And I then entered university and, and I always thought about it. And when I started to learn about molecular biology and DNA and, you know, the blueprints of life, I thought this is where we need to hit disease. We need to find a way to treat it at its root cause.

[00:04:15] I said, instead of going into medicine, I'm going into research because I don't want to treat people at the end of their life. I want to prevent them from getting to the point where they are that sick. So, that's set me on my journey.

[00:04:28] **Stephen Calabria:** What are some of the key principles behind gene therapy and how it can be applied to cancer treatment?

[00:04:35] **Brian Brown:** So when I started gene therapy was really this idea of what I guess I would now call gene replacement. So it's the idea that you were born with a defective gene, and we can synthesize a normal copy of that gene and then introduce it back into the person.

[00:04:52] So we replace the gene that was defective. In 20 years, gene therapy has spread out to many, many different modalities so, that didn't exist, not even in science fiction writers' eyes and thoughts did we have some of these ideas like RNA interference and CRISPR and CAR-T cell therapy.

[00:05:11] These are all really relatively new. So, gene therapy is kind of a broad class. Actually, the term isn't really even used as much anymore. So I often refer to it as RNA and DNA therapeutics.

[00:05:23] And it's really the idea of using nucleic acids to treat disease. So instead of using small molecules like we've been using for 40, 50 years as drugs or even antibodies like we've been using for the past 30 years, we use nucleic acids.

[00:05:39] And this can still be gene replacement, but we can also use nucleic acids to do things like create a vaccine or we can use nucleic acids to turn off a gene.

[00:05:49] So these are all different forms of, I guess, under the broad umbrella of gene therapy or RNA and DNA therapeutics, but it's really this idea of using nucleic acids as a drug to do different things to treat D disease in different ways.

[00:06:04] **Stephen Calabria:** Are you researching any specific types of cancer in relation to gene therapy, or could this apply basically to all cancers?

[00:06:12] **Brian Brown:** I think that the appeal of gene therapy for me and, really the beautiful thing when we think about it, it's a really platform type of system because nucleic acids, we know the code of life.

[00:06:24] We know the code for producing different genes. And so once you hit on the right platform, you can almost do plug and play. So a good example that people already understand or heard about in the news all the time is the COVID vaccine.

[00:06:40] So they came from a type of gene therapy, it's an RNA approach. And they were already making these RNA vaccines for cancer. When COVID came along, they said, okay, well, let's just plug in the sequence for the SARS CoV 2 virus, the spike protein, and now we can make an RNA vaccine. And sure enough, it worked.

[00:06:59] So, it's the same thing with the work we do in cancer. We're trying to develop both mRNA types of approaches for reprogramming a tumor from what we call immunologically cold to immunologically hot, and we're also developing these gene and cell therapies where we engineer T cells to go and attack tumors.

[00:07:18] So, the question was, are we doing it for a particular cancer? And the answer is the therapies that we're trying to develop should be widely applicable to many different types of cancers because the principle of what we're trying to do, which is engineer the immune system, is the same for all cancers.

[00:07:35] And the modalities we're using, which are either mRNA-based approaches or CAR T, they can just be fitted for different types of cancers. We just have to change the nucleic acid sequences and we can apply them to different types of cancers. So really broadly applicable types of approaches.

[00:07:51] **Stephen Calabria:** To the non scientific community, the world of scientific research might seem pretty dry and rather prosaic. In what ways does your work, would you say, require resilience?

[00:08:05] **Brian Brown:** I hope it's not dry and I hope, you know, maybe if that's the case, then we're not communicating it well. So, um, I'm happy to, uh,

[00:08:13] **Stephen Calabria:** Please dispel that.

[00:08:13] **Brian Brown:** I'm happy to dispel that because I, I think , it's one of the most exciting things when you unlock and when you learn about how life is created, how life evolved, how drugs work, how, how your eye works.

[00:08:28] I mean, this is the most exciting thing and I hope people don't find it dry. In terms of resilience, I think all of science, doing scientific research, requires resilience. It is. a field where 90 percent of things will fail because we are at the edge of knowledge.

[00:08:45] I mean, that's the whole purpose of science and of research is to learn new things about the world, to create new things that haven't been created before. And when you do that, you're not going to get everything right.

[00:08:56] So there is an absolutely necessary resilience to scientific research, because you have to be prepared to fail a lot. You have to be prepared that, you may think you're smart and nature's going to prove you, you know, you may not be so smart that you understand how nature works.

[00:09:10] Or you may have an idea and you go test it in the lab and it turns out to be an utter failure. And, that's going to knock you on your butt. I think that there's another type of resilience particular for gene therapy. So, I got into the field, I started in gene therapy in 1998.

[00:09:28] And at that time I thought, oh my god, I'm almost late. You Everything's going to be cured by the time I finish my PhD, it's all going to be done. And starting in 1998, there was really a lot of hype in gene therapy leading up to 1998. There was no successes yet clinically, because few things have been tried in the clinic.

[00:09:46] And then the, almost one of the first things they put in the clinic not only failed to have any success in terms of treating the patient, but one of the patients died in the trial. And that was a big, big stain on gene therapy's promise. So then, still no successes that not only failure, but tragedy occurred.

[00:10:04] And then in 2000, there was one success that came out of a hospital in France. Two years later, that success turned into tragedy when several of the kids developed leukemia. So, by around 2002, the field had gone from great hype to basically people kind of jeering it as like all hype and no substance.

[00:10:24] And it was a failure and money had been wasted and gene therapy will never work. Like I had people repeatedly tell me gene therapy is done, it's been tried and it won't work. By 2003, I was starting my postdoc and being told over and over this field is a failure.

[00:10:41] So it required a lot of resilience because at the time I even felt, I'm not even going to get a job at the end of this. Even when I started here in 2008, the field still had really no, or very few successes.

[00:10:53] Actually, one of the only successes in the entire world of gene therapy had occurred in the hospital from the group that I had been working in,

in Milan. So I did have some access to an understanding that it could work very well.

[00:11:04] But it was still getting knocked down, grants getting turned down because the field wasn't good. Even being told, don't put that you work in gene therapy on my website, because it will turn people off.

[00:11:15] So, I think that going back to this, all science requires resilience. And part of that resilience is not only because you personally see failure, but you're told over and over that things won't work.

[00:11:27] And, you know, I think we often hear stories about scientists who one day became famous after years of failure. And you think, Oh my God, of course that was going to work all along, you know?

[00:11:38] But at the same time, when you're going through it, And being told, living through being told what you're doing has no meaning, it's never going to work. That's very, very tough and requires resilience, but the payoff is great.

[00:11:51] I mean, I think it's worth it. And I think that, if it wasn't hard, we would have already solved the problem. So I think that's where resilience comes in.

[00:12:01] **Stephen Calabria:** Are there any examples of major challenges or obstacles you encountered in your research? And if so, how did you address them?

[00:12:09] **Brian Brown:** I think there goes from everything from running a lab and finding the right people, that's a big challenge still to this day, you know, you want to find bright, hardworking people, and that can be tough.

[00:12:21] Getting funded is a challenge, for the reason that you have a vision. You try and convince people of your vision, but there's other smart scientists out there who have decided not to work on what you're working on.

[00:12:33] And so when they read your grant, they are naturally skeptical because if they weren't skeptical, they may be working on what you were working on. So that's always a challenge.

[00:12:41] In terms of actual lab research, yeah, we've had lots of failures in the lab, lots of ideas that we thought would work, directions we went. But you know, even when 90 percent of things fail, those 10 percent of successes are

significant and impactful enough that it takes you in a new direction and you still reach your goal.

[00:13:02] I think, there's two ways that we do science or not, there's more than two, but in terms of the way we do science.

[00:13:08] So there's biology work, where we just want to understand how nature works. And there's lots of times when you have an idea of how biology works, of how nature works, of how one molecule will interact with another molecule.

[00:13:23] Sometimes you're wrong, but then determining that you're wrong still answers a question that can advance science. With bioengineering, with developing new gene therapies, when you're wrong, it just gets thrown in the trash, right?

[00:13:36] So it's not like if you have an idea for what can cure cancer and then you go and develop it and you put it into, let's say, not into the patient yet, but you, well, sometimes you put it into an animal model, that fails, sometimes it works in an animal model, then you take it to the human, and then it fails in the human. Well, that's done.

[00:13:55] I mean, it's not like you advanced, the only thing you advanced is that that system that you did doesn't work. So as a bioengineer, we think a lot about achieving that goal, and it's fine to have a lot of failures as long as you find the direction that it takes you towards getting a solution.

[00:14:11] So there is no right or wrong answer. Sometimes there's no one way to get at a goal. We don't care how we get there. We just want to achieve that goal. And sometimes, the highest goal for us is curing a particular disease, whether it be cancer or diabetes or heart disease or hemophilia.

[00:14:28] That's our goal. So, we have failures on the road to there, but then when we get there, those successes are monumental for us and for our patients.

[00:14:36] **Stephen Calabria:** To continue with what you just touched upon, how do you approach designing and conducting clinical trials for gene therapy treatments in cancer patients?

[00:14:46] **Brian Brown:** So, I don't run clinical trials myself. I work with people who do run clinical trials. In fact, at Mount Sinai, one of the wonderful things, and, and I think truly special things, that is quite unique really in the

country is how closely the PhD scientists and MDs and MD PhDs work together.

[00:15:05] And we do that daily here on this floor. There's a mix of, on the floor we're on right now, there's a mix of scientists working from basic translational and clinical. And we talk about clinical trials all the time. I think it works in two ways.

[00:15:18] So there's one, the clinical trial, but I'm going to go back one step, which is, what do we do in the lab, right? What's my job to research, right? What am I looking to discover or to create?

[00:15:30] And that comes from talking to the clinicians who see patients every day and who tell me what's working and what's not working. So, me as someone who thinks about bioengineering, I want to know what problem to solve.

[00:15:43] So I go and talk to my colleague Josh Brody or Tom Maron or Dimitri Zamerin and we discuss what is not working in patients. What can I do to study that in the lab, to solve that problem.

[00:15:56] They tell me this drug is causing a lot of liver toxicity. I can go back in my lab and think about how can I target the therapy so it doesn't hit the liver. These are the type of things that I think about.

[00:16:07] And then, you know, we go back once we have a solution for the problem, then we go back, we talk to clinicians, we see if this would work, and then we test it in different ways, and then we bring it to the clinic in the safest possible way, where we want to design the clinical trials that will test whatever new kind of treatment we've developed, but that makes sure that the patients, first of all, will not suffer any harm.

[00:16:33] That's obviously paramount to the way that we design it, but also that they'll continue to receive the best possible treatments. And we think about this all the time. So, usually we design, if we are doing something like when gene therapy first started being put into humans, especially for cancer, we take only patients who have failed every other drug that's out there.

[00:16:55] So, tumors that are not responsive, and we will then put those patients on a trial where we may not know the outcome, but we know from everything that we've treated them with, from every experience that that patient is, probably only has a few months left to live.

[00:17:11] And so we are going to try these more experimental measures, and that's usually the start of a very new type of therapy. Then, as the therapy progresses, so we put it into patients, and then we start to see a signal, like, we start to see it working.

[00:17:26] Sometimes it works absolutely amazingly well, and, , or sometimes it works amazingly well just in a very small fraction of patients. Then the next steps is, we start to think about how we can move the therapy earlier in the stage of treatment for the cancer.

[00:17:42] **Stephen Calabria:** What safety considerations are involved in developing gene therapy treatments for cancer?

[00:17:47] **Brian Brown:** Yeah, there's always been something about gene therapy where, for right or wrong, that sort of captured both the imagination of people in terms of what it can do, but also concerns about what it can do.

[00:18:00] Starting, actually, in the 1970s, way before gene therapy was even performed in a Petri dish, the FDA and the NIH and the U. S. government formed recombinant DNA advisory committees because people were so concerned about the potential of this new form of medicine and what can be done with it.

[00:18:18] So this is really something that's been thought of for a long time, because we think about, you know, what's almost the most sacred, one of the most sacred things to our being, you know, is, okay, one is our consciousness and another is really our DNA.

[00:18:30] We think, it's what our parents passed down to us and that's what their parents passed down to us. So when we think about manipulating DNA, it's in our thoughts that we have to be very, very careful with this.

[00:18:42] So that started a long time ago. And I think now over 30, 40 years, we've sort of come to understand that we can make modifications of DNA in cell culture in even in a person by delivering replacement DNA without affecting, really, their entire DNA of their body and especially not of their germline.

[00:19:02] So one of the first considerations was, would whatever I'm doing affect what they could pass down to their kids? And the answer is, resoundingly no. So we're really only modifying a person, drugging them in a way that

doesn't affect them generations or even the next generation. So, that's one consideration.

[00:19:21] And then, of course, we think about, we don't want to deliver anything that could be spread around. So we think about that because one of the ways that we perform gene therapy, or we used to exclusively, but not anymore, but we used to deliver it using inactivated viruses.

[00:19:34] So, these were viruses that couldn't replicate. We removed all the guts from them and we just use them as a delivery vehicle. And so it was early on consideration for safety was like, is this absolutely a non replicating way of delivering DNA?

[00:19:49] And then, of course, in the past, really three, four years, I mean, starting, I guess, 10 years ago, but really in the past three, four years is we've now started delivering DNA and RNA using non viral means, using these vehicles called nanoparticles.

[00:20:06] Really, really powerful new form of medicine that's has proved to be very, very safe and effective. So, these are things we think about. We think about, also, acute toxicity. So, if you deliver it, are you going to trigger a very toxic event in a person that has the potential to kill them immediately? That's what happened in that trial in 1998.

[00:20:25] For the first gene therapy trial, they injected young man with an adenovirus and it triggered the immune system in a way that caused a really, really rapid inflammation that ultimately killed him, unfortunately.

[00:20:37] So we think about all these things and, over time and over many, many clinical trials, we've really learned how to mitigate a lot of the toxicity of these things, or almost all of it, so that it can be done very, very safely, even outpatient.

[00:20:52] **Stephen Calabria:** Ethical concerns, I imagine, may also arise in your work, particularly as it relates to cancer treatment. What are some of the ethical issues you encounter and how do you navigate them?

[00:21:06] **Brian Brown:** We never do anything that's related to young children or people who couldn't consent. We never do anything that we're not developing anything that that would be passed down for generations.

[00:21:17] So I think those type of ethical concerns, I don't think play a role anymore. I mean, just because of the way we do these things and the people who are treated, right? So, vast majority of people who have cancer are adults who would consent to whatever treatment would be given.

[00:21:35] I think in terms of probably the major ethical concern that we do think about and does worry me and even makes me think about how we develop these therapies is, people's access to the medicines.

[00:21:47] That's probably the biggest one. So, we want to make sure that whatever we're developing, will be able to be utilized by everyone and we don't want these therapies to break the bank of a family who needs them and cancer patients who are in need.

[00:22:03] So I think that these are early days. So, for sure there are gene therapies that are very expensive. And, thankfully, there are systems in place to help people pay for those insurance companies. So most people are not being denied these therapies right now.

[00:22:23] But there are therapies that are tough to get. And I think that we do have to have a little bit of patience. Because, just like the first generation of car or phone may cost a lot of money as we reach economies of scale.

[00:22:39] If you think about some of the things that you can buy on Amazon, electronics, drones, like this is like a technology, a drone. I've never bought a drone, but a drone, you know, I think was like hundreds of dollars just a few years ago, and now you can probably buy a drone for like 50 dollars.

[00:22:54] So, I think as gene therapy becomes more ubiquitous, as more and more companies get into it, as there's competition in the area, the cost will come down, especially as we build economies of scale. So what do I mean by that?

[00:23:06] Well, I said before that gene therapy is a platform technology. So the M. R. N. A. vaccines are a good example. We invested a lot of money to make sure that, you know, a billion people could get an mRNA vaccine, and that brought down the cost tremendously of making them.

[00:23:24] And now that we have the capacity to do that, we can fit in a flu vaccine or we can fit in a cancer vaccine.

[00:23:30] And the cost to do that is one-tenth of what it would have been five years ago before we developed these economies of scale for manufacturing

mRNA vaccines, and before we had hundreds of labs and dozens of companies that have gone into this area that create competition to make a better product and bring down the price.

[00:23:51] And I think that, your question was about ethics, so that's the ethical concern I always have, which is, I don't want to make a therapy that three people could afford. So, we hope that we are making things that will be usable and advance society in a way that benefits everyone.

[00:24:08] **Stephen Calabria:** Collaboration and social support are often crucial in scientific research as well as resilience. Could you talk about the role of collaboration in your work generally, and collaborations you've formed with other researchers or institutions to advance your work?

[00:24:25] **Brian Brown:** Collaboration is everything in science. So, I think one of the biggest misconceptions of science is, kind of this lone scientist idea. Even when we think about the Nobel Prize, so the way history records scientific discoveries is often, you know, oh, who invented insulin?

[00:24:45] Or, you know, who discovered CRISPR? And, you know, you go back and you take the two to three people, or one to three people who won the Nobel Prize. This is not how it works at all.

[00:24:56] Every single scientific discovery is based on a body of work that is ongoing, that is going on from many dozens, hundreds of labs around the world. Everything is built on prior work.

[00:25:12] So, there's a famous Newton quote, if I've seen further, it's by standing on the shoulders of giants. And I think that applies to science, which is, not only are we using past work, but we're using work that our collaborators, people that we may not even really think about collaborating with, but that are on the floor above us and we run into them and, or we see them in a seminar give a talk and then it sparks me to do something in my lab.

[00:25:38] And so science, it works in this way that it's really about taking the limits of knowledge, what's already been discovered, and then cross pollinating from what's going on in some other field.

[00:25:50] That is one of the ways we innovate. So I can't stress enough how important collaboration and team science is. And also that, the way discoveries are made, all discoveries, it's really organic. So it's not like one person is a field.

[00:26:05] It is really a field of science, a drug that is made is the product of hundreds, thousands of people who sometimes are working together, but sometimes don't even know each other and yet have influenced each other in different ways.

[00:26:20] So I think there are collaborations that are seen and unseen because we have connections with people just from reading someone's paper. I mean, am I collaborating with them? No, but I read their paper and it inspired my work.

[00:26:33] It changed what I did in my lab. So I may not have called them up on the phone and collaborated with them, but I'm collaborating with them through their body of work that I'm reading and it's influencing me in my lab.

[00:26:43] And then there are direct collaborations I have where, my good colleague, Miriam Merad, we collaborate, we speak almost every day and, and we collaborate through shared projects and ideas, complementary ideas that we have together, and we help set people on projects in the lab, and then, not only do I collaborate, but the people in my lab collaborate with each other.

[00:27:03] They collaborate with labs beside them. So I think it's really fundamental to how science works, is that there's kind of this organic process that exists where lots of life forms are working together to get to an end and make a discovery and advance science and advance therapies for the clinic.

[00:27:23] **Stephen Calabria:** What do you see as the future potential of gene therapy and cancer treatment and what advancements do you anticipate in the coming years?

[00:27:32] **Brian Brown:** So, the future, we will get to a point where the future for gene therapy is, it can be the modality that results in curing cancer patients. This is what I think. So we're not there yet, but I'm not just saying that.

[00:27:45] It's based on what we are seeing already. So, there is a type of gene and cell therapy treatment called CAR-T therapy that is, so far, being used very, very effectively in leukemia, lymphoma, and myeloma.

[00:27:59] Those are hematological cancers, so blood cancers. And, there are patients who have been treated with this gene and cell therapy where they're cured for years. I mean, they're effectively cured.

[00:28:11] The doctor- we tend not to like to use the cure word because, often, cancers can come back, but we just see tremendous success there.

[00:28:18] Now, those therapies haven't been as successful in solid organ cancers like lung cancer and liver cancer, kidney cancer, but it's getting there and I think what makes the potential of gene therapy so limitless is this, I mean, it's very simple, which is you and I sitting here are a product of our genes, right?

[00:28:39] So, you're built by DNA being transcribed into RNA, being translated into proteins. That is making my lips move now. It's making my eyes see everything in this room, it allows me to pick up my phone, it allowed the person to invent this phone, , is that your DNA is able to do this.

[00:28:58] It encodes blueprints and it allows a person to basically do everything that they do. Now, we don't understand exactly how the blueprints end up resulting in this very complex thing that is a human, we don't understand every aspect, but we know that it's possible.

[00:29:13] So, as an engineer, bioengineer, we can think about, well, if the DNA has that capacity, can I use it to do things like create a cell that will go and find every cancer cell and kill it?

[00:29:26] That's a simple problem, almost, compared to all the amazing things that DNA and RNA have already evolved to do in us. It's a matter of learning how the system works, learning why some cancers resist, and then engineering the system to overcome that.

[00:29:46] And it does require trial and error. I mean, we tend to, as humans, you know, our lifespan is not that long. So we look at things like, Oh, you know, you guys told me you were going to cure cancer 10 years ago. It's still not cured.

[00:29:56] Well, 10 years is a pretty small time, right? So, I think that the future is extremely bright. Discoveries and research advances tend to be exponential. So we overcame a hump between 2010 and 2020, just an amazing hump because nothing in gene therapy, not nothing, but very few things were working up until 2010.

[00:30:15] Huge explosion in 20, between 2010 and 2020, in terms of both seeing gene therapy work in the clinic, but also the new types of gene therapy. I mean, CRISPR, this way of editing genes, which is different than just replacing genes, but we can actually edit them.

[00:30:31] We can change nucleotides. That didn't exist before as a therapeutic modality or even a technical modality before 2010, now it's already in patients and two have been FDA or at least one have been FDA approved.

[00:30:43] So we are in early days and the potential, I think, is limitless because in the same way that silicon and steel have been able to create robots that are coming closer and closer to reproducing human abilities, we will be able to do the same thing with genetic engineering.

[00:31:00] We will be able to create, maybe not fully-fledged humans, but we'll be able to create biological systems that can replace a pancreas or can repair damaged neurons or can go in and, and wipe out cancer cells.

[00:31:12] That's entirely possible, I think within the next 10 years some of these things will happen.

[00:31:18] **Stephen Calabria:** You mentioned the time period from 2010 to 2020, what gene therapy advancements came about as a result of research into COVID?

[00:31:28] **Brian Brown:** So, COVID in particular was really the COVID vaccines. So, there was that technology of mRNA vaccines, that concept, like, could we use mRNA as a way of vaccinating started in the 1990s.

[00:31:42] And there was a group of people, not one, not two, but dozens who thought this can work. We can make this into a vaccine. And in the early, you know, aughts and the early part of the 2000s, that was a very fringe group of people, not fringe like crazy, but very few people working on it.

[00:32:04] But they really believed it. They were resilient. I mean, very few people thought it could work. And actually, the COVID vaccines, the most successful ones, were based on RNA. People in the early aughts thought it was going to be DNA that could make a good vaccine.

[00:32:18] But the people persisted. Grants rejected and you know, all these things and people telling them it wouldn't work and then continue to do it. And they had more and more success. They found ways to make it work better.

[00:32:30] And then the really big bang moment came during COVID, because you can make these vaccines so quickly. Now, pandemics don't come, thankfully, don't come along that often. And, we generally have time to make viral vaccines, pathogen vaccines, because we see the pathogen coming.

[00:32:48] So, COVID really hit us almost out of nowhere and they had to make them quickly. Cancer, on the other hand, that is something where, you can be diagnosed with a cancer, like pancreatic cancer, and die two weeks, three weeks, six weeks later.

[00:33:04] Like you didn't even know you had the cancer. You felt sick, you go into the hospital, and then six weeks later, you could pass away. And so, in that type of situation, like cancer, you need to be able to make the therapy very, very quickly.

[00:33:16] So what's very exciting about the mRNA vaccine technology, in the same way that scientists were able to make a COVID vaccine in a matter of weeks, we can do the same thing, even a matter of, yeah, less than two weeks, you could make a cancer vaccine for a patient, and that is really personalized cancer vaccine.

[00:33:35] That's a really, really powerful. We're seeing success in the clinical already now from. Trials that are being run by Moderna and BioNTech. They're not the only companies working on it. They're not the only groups working on it.

[00:33:46] So, again, we're scaling this up and we're getting more minds thinking about how can I make better vaccines for cancer, for other types of infection, for autoimmune disease, which is the flip side of cancer.

[00:33:59] So in cancer and infectious disease, the immune system is not working well enough to fight off these things, and in autoimmune disease, you have the immune system fighting a person. It's actually attacking the person.

[00:34:10] So, people are trying, including my lab, trying to develop mRNA vaccines that educate the immune system to no longer attack itself and to try and cure autoimmune disease.

[00:34:22] **Stephen Calabria:** Can you describe a particularly challenging experiment from your research that informed your approach to gene therapy, particularly with regard to cancer?

[00:34:32] **Brian Brown:** So, I think that one of the things that was eye-opening for me, and this started many years ago, how important it is for delivery and targeting of these modalities. So, we can create, synthesize in the lab, any DNA we want.

[00:34:53] We can synthesize DNA to encode any protein we want. We can really, or mRNA, we can make it encode different proteins, spike or something to turn a cancer hot. But how do we get it to the right place? That is a fundamental problem.

[00:35:10] It's such an important challenge. So in my work, we saw that we could make something in the petri dish, but could we get it to where we want it? And we also saw that when we got it to the wrong place, it can have really negative consequences.

[00:35:25] Actually, getting it to the wrong tissue. So let's say you have an mRNA that encodes for a protein that is so toxic, it will wipe out all cancer cells. It would be curative, if you can get it into the tumor. But what happens when it goes to the liver?

[00:35:41] Well, that's a problem because the person or the animal will die. So, in my research we saw this, and it was profound, because we had a treatment that we knew could work extremely well, but it failed, and actually was even toxic, because it went to the wrong place.

[00:35:58] So, that led me on a mission, which still continues in my lab, which is how can we improve the delivery and targeting of nucleic acid therapies? And it is probably one of the most important problems to solve in, I would go so far as to say, all of medicine.

[00:36:16] And I like to say if you solve delivery, you solve medicine and, I say that because you know, probably not all disease but if you can find a way to deliver treatment just to the regions where there's Alzheimer plaques or just where there's cancer cells, or if you can find a way to just target your therapy to the T cells killing pancreatic beta cells and causing type-1 diabetes, then you would cure that disease.

[00:36:42] You would cure all these different diseases if you can target just the diseased area of a tissue. And so we think about that a lot.

[00:36:51] And we've seen it in the lab and now we're trying to develop ways to solve that problem and not just us but many groups around the world and we're seeing amazing progress in this area that is going to transform diseases that can't be treated right now with current therapies because it would be too toxic to applying these types of drugs in all kinds of diseases with little or no side effects.

[00:37:14] **Stephen Calabria:** What scares you most as a scientist?

[00:37:19] **Brian Brown:** It's very important that the public understands what science is doing, the importance of science, and how it's advancing society, because ultimately, at least the way I think about science, is that it is a public endeavor.

[00:37:33] It is there not to hurt society, but to help society. And it's also funded by society. It's funded by tax dollars in some cases or companies in other cases. Philanthropy.

[00:37:45] And it's very, very important to me that society continues to understand the progress and the advances and the help that is being made by scientific research from basic research that people may not associate with having advances, like there are people studying how enzymes work in bacteria in thermal baths in Iceland and people may not associate that, well, how is that curing cancer?

[00:38:08] Well, that enzyme that they may have discovered could be then used as a drug. And in fact, actually it did happen that one of the enzymes we discovered in one of these bacterias is used for a test called PCR that we use all the time, that people may not have thought initially was important.

[00:38:22] So that's the basic side where the advance may not be obvious. And then there's the translational, where we saw with the COVID vaccines, fairly large fraction of society was just so put off by them. It became political. Maybe there's many reasons it became political and you can't draw a lesson from everyone.

[00:38:41] But at the same time, that was scary to me because I come to work every day and I really think about my job as trying to help people. think that I'm trying to do science so that someone's sick parent or grandparent can be treated and can have an extra 5, 10, 20 years of having family dinners together.

[00:39:01] And so it, saddens me when there's kind of this either politicization of science or where there's kind of a fear of what science is doing, which can happen. I mean, I don't want to say that there can't be negative consequences of certain things that we've done with science.

[00:39:18] I mean, I think we're seeing climate change as a consequence of some of the advances of industrialization of the world. And that came from scientific discoveries. You know, we invented the car, we invented the plane,

and now that's leading to climate change, but my strong belief is that we can also use science to address those problems.

[00:39:39] We can create cleaner energy sources and the same thing in scientific research, there are problems that may be created by modern life. Honestly, I think that people don't realize when people say, Oh, you know, heart disease has gone up or cancer, you know, the rates of cancer have gone up.

[00:39:57] Often the cause of that is that people are living longer. And so, it's not like, people are not getting cancer more because there's some toxin in the air or something that we've created.

[00:40:09] I mean that does happen, but a lot of times people are developing these diseases because people didn't live till 90 or 100, 200 years ago, or even 100 years ago.

[00:40:19] So this is happening because we're able to live longer, and that's a good thing that we're able to live longer. We're also able to live healthier, thankfully. So as we are allowing people to live longer because we've developed, better lifestyles, less smoking.

[00:40:32] There's stenting. It's a way to keep people alive longer because it's allowing their heart to function better. So, cancer crops up and now we have to find treatments for cancer to improve the quality of life and the longevity of people.

[00:40:45] So, it only scares me if people don't understand what we're doing or if science stops serving society or there's a backlash against it.

[00:40:56] And, that's happened many times in history. And we don't want that to happen again. So it's very important to me that scientists educate people properly and honestly in terms of what we're doing.

[00:41:11] **Stephen Calabria:** What advice would you give to aspiring researchers, particularly those interested in a career in gene therapy?

[00:41:18] **Brian Brown:** We need bright, innovative minds to come into the field. There are still so many problems to solve, so many challenges, so many new things to be discovered that we need the best and the brightest to come into the field.

[00:41:34] And I think that an important piece of advice, one is resilience, because things will fail and you have to be ready for that. But just keep going because progress comes from failures and then new attempts at doing things.

[00:41:47] So I think that this is how we make progress in society. But I think that almost all problems can be solved. And so, I think that there's a tendency to think that, Oh, we'll never cure cancer. But, I think that's not true.

[00:42:03] I mean, you know, we've seen so many diseases. I mean, sometimes there's like a point where you're like, This is the hardest cancer that, we'll never fight it. Lung cancer. Smoke, people who are like 30-year smokers, coming up with like stage 4 lung cancer.

[00:42:16] Like, that's a death sentence. There's no way. And then along comes immunotherapy, and now 20 or 30 percent of those people who would have been told they only have six months to live, eight months to live, are getting three, four, five, sometimes ten more years of life.

[00:42:30] So, and that came through this scientific endeavor, through engineering better antibodies and finding the right targets through a mix of biological studies and biotechnology. So, if you ask what is my advice to aspiring researchers, it's that we can solve these problems.

[00:42:50] And I don't think you should be scared off, you should come into the field and come up with new ideas, new ways to develop better therapies for treating diseases that we think are incurable now, but will be curable by, you know, with enough, thought and ingenuity going into finding new treatments for them.

[00:43:10] **Stephen Calabria:** Last question. What do you wish more people knew about science and scientific research?

[00:43:17] **Brian Brown:** I think, you know, one is, it's so easy for us to forget almost right away, what we have now that we didn't have five minutes ago, even. Like, we so quickly forget what is a product of scientific research and we take it for granted.

[00:43:34] Discoveries and it just gets fitted into our daily lives all the time. I mean, the stupidest things like, even the way we take pills now, they make them taste better and they're smaller and like all these things that, you know, you'll just have to talk to someone who's older and they'll be like, ah, when I was

young, you know, we had to take them by suppository or some crazy thing like that, or by needle injections.

[00:43:54] So, type one diabetes is an amazing example because this is a disease where, 20 years ago, to find out what your blood sugar was, you had to pee on a stick each time and then it went to like these blood sticks where you had to, like, poke your finger and take blood every time and now you can wear a sensor, a patch on your arm.

[00:44:12] It requires a tiny, tiny needle every 10 days, but then you can look at your phone and it tells you your blood sugar. And then within six months, a year, it's going to be like, you don't even have to put that needle in.

[00:44:21] You can have your phone touching your skin and it's going to tell you. Well, we'll soon forget where we were before that.

[00:44:26] And there will be a generation of people who didn't even know what it was like to not have that. And I think that, it's not like I want people to remember, but I think that when the public sort of says, well, what is science done for us lately?

[00:44:37] I think that they should realize, these advances that, with certain negative things comes ten or a hundred positive things, and I hope that people realize that.

[00:44:48] I also think like, going back to this passion of mine, which is to try and get more people into science and from broader backgrounds, one thing I say to the high school students when I go and speak to them is, I think there's a misconception of what a scientist does, based on what science is like in high school and university.

[00:45:09] People are like, Oh, science is hard or science is like a lot of memorization.

[00:45:13] **Stephen Calabria:** Or prosaic and boring.

[00:45:14] **Brian Brown:** Yeah, prosaic and boring. Yeah, exactly. And it's not the case at all. I actually think in the same way that probably legal shows and police procedural shows overdramatize, or make maybe more exciting, the life of a lawyer, not to take anything away from a lawyer or policeman or anything.

[00:45:32] I think that probably the life of a scientist and what they do is probably not conveyed so well, maybe conveyed more boring than it is, because it's actually a super exciting job. You get to talk with people all the time and bounce ideas off them and then go and test them in the lab and it's really nothing like high school science.

[00:45:50] It's filled with exciting things and, yes, there's a lot of things that fail, but so many things, you know, when you see it work, it's just the most amazing thing. And, and it's so rewarding as a career.

[00:46:01] **Stephen Calabria:** That was it for my questions. Was there anything else you wanted to say?

[00:46:04] **Brian Brown:** No, thank you.

[00:46:05] **Stephen Calabria:** Dr. Brian Brown, thank you so much for coming on the show.

[00:46:07] **Brian Brown:** Thank you. It was a great pleasure. Thank you very much.

[00:46:10] **Stephen Calabria:** Thanks again to Dr. Brian Brown for appearing on today's show.

[00:46:14] That's all for this episode of Road to Resilience. If you've enjoyed it, please rate, review, and subscribe to our podcast on your favorite podcast platform.

[00:46:22] 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.