Dr. Mariam Hanna:
Hello, I'm Dr. Mariam Hanna, and this is The Allergist, a show that separates myth from medicine, deciphering allergies and understanding the immune system. Ten years ago, if a child was born with a severe genetic immune disorder, our options were limited. We could treat infections, we could support the immune system, and if the circumstances were right, we could attempt a bone marrow transplant.

But we couldn't fix it. We couldn't fix that gene. Meanwhile, in the oncology space, technology was developed looking to fix a very similar problem.

Five years ago now, I listened to an oncologist as he discussed CAR-T versus stem cell transplantation for blood cancers and thought it was science fiction. Reality is changing in oncology, and in immunology as well. Scientists are learning how to edit that genetic code, correcting the mutation responsible for a disease, or addressing that specific cell line.

Gene therapy is rapidly moving from the laboratory into clinical trials for patients with inborn errors of immunity. And for a field built around a single gene disease, that shift has the potential to redefine what treatment, and even cure, might one day look like. To help us understand where this field is headed, I'm joined by an expert who works with the intersection of immunology and deals with the most transformative therapies in modern medicine—gene editing.

Dr. Nicola Wright completed her fellowship training in pediatric hematology oncology with a focus on immunology at the Cincinnati Children's Hospital Medical Center and Stanford University. She now practices benign hematology and clinical immunology at the Alberta Children's Hospital and holds the Barb Ibbotson Chair of Pediatric Hematology. Dr. Wright is co-chair of the Inborn Errors of Immunity Registry Steering Committee in the Clinical Immunology Network Canada, or CINC. Her research interests include developing a platform for gene editing for blood and immune disorders, and she's an advocate for increased gene therapy access, and we'll talk about the problems with that, and clinical trials for rare pediatric disorders in Canada. Dr. Wright, thanks so much for joining us today, and welcome to the podcast.

Dr. Nicola Wright
Thank you so much for having me.

Dr. Mariam Hanna:
All right. We're going to get you to start by explaining to us what we actually mean when we say gene therapy in the context of inborn errors of immunity. What are we actually talking about here?

Dr. Nicola Wright
Great. So I think gene therapy falls under the umbrella of cellular therapies, so that would include things with cellular therapy like viral-specific T-cells or CAR T-cells, and then the gene

therapies is in inborn errors of immunity, generally what we're doing is we're editing bone stem cells or hematopoietic stem cells to fix an inborn error, so patients have a pathogenic variant that causes their underlying immune deficiency.

So we're going in and fixing that, either providing a new gene, correcting a spelling error, or sometimes in some diseases we actually fix something peripheral that will then fix the disease with a variety of different technologies.

Dr. Mariam Hanna:
That's incredible. That's even possible. And for those of us that have been so used to the word just transplant as the definitive therapy in these diseases, how should we start thinking about gene therapy fitting in here?

Dr. Nicola Wright
So transplant is almost a poor man's gene therapy. So what we're doing in bone marrow transplant is we're essentially blowing out the child's own bone marrow stem cells, the one who has the inborn error of immunity, and we're taking the healthy bone marrow stem cells from another person and giving those to the patient. So we need to use a lot of conditioned chemotherapy and immune-suppressive drugs.

So through that transplant process, that is toxic. They lose their hair. They have mucositis, so they have trouble eating, sore mouths, diarrhea, those sorts of things.

They also need support with blood transfusions and things through that process. There's long-term consequences of that chemotherapy. And then after their transplant, they can also develop things like graft-versus-host disease.

So bone marrow transplant comes with a lot of side effects to get that new healthy gene in there. When we're talking gene therapy, most of the gene therapies that we've done so far have been what we call ex vivo gene therapy, where we take out the patient's bone marrow stem cells, we take them to the lab, and we either put in a virus that's got the proper gene in there, or we use gene editing technologies to fix the gene, and then we give them back to the patient. They're still needing some chemotherapy, so busulfan is what's typically used, but it's about a quarter of the dose of what's used for bone marrow transplant, so less toxicity, and it's only busulfan, whereas in most bone marrow transplants, we use two to three different agents.

The other thing with the gene therapy is we don't need to find a donor, and after it's done with it being the patient's own cells, we don't have to worry about graft-versus-host disease. If you look at gene therapy that's been done for a number of diseases, like ADA-deficient SCID is probably where the most patients have been done. There's been over 100 patients treated with that.

The outcome for those patients is 100% survival, and over 90% of them have good immunoconstitution afterwards, whereas we can't say 100% survival for bone marrow

transplant, so in my biased opinion, I would say that the gene therapy is actually safer and in some cases more efficacious compared to bone marrow transplant.

Dr. Mariam Hanna:
But I want you to deal with me like the average fresh grad and give me our TikTok version of mapping this landscape of the different mechanisms that we have for the gene therapies that exist today. Hit me with your best TikTok on this one, Dr. Wright.

Dr. Nicola Wright
Sounds good. Old therapy, we used a virus that was called the gamma retrovirus. There were some problems with that, so that's been ditched for the most part.

And then the next one is a lentiviral gene therapy, and that's where you take a normal gene and you insert it into a lentivirus that's been modified in a variety of different ways. And to do gene therapy with a lentivirus, so for example, like with ADA-deficient SCID, you take out the patient's bone marrow stem cells, and then in the lab, you essentially infect them with this lentivirus. That virus will then insert that healthy gene into the patient's stem cell DNA, and then you give those stem cells back.

And that's the most common one that's been used. I think a lot of people have heard about CRISPR now. It's in the news a lot.

We're now moving for some diseases into using things like CRISPR. So CRISPR is a technology where you can actually edit the gene. So the CRISPR mechanism goes in, it makes a double-stranded DNA break in the DNA, and then inserts a chunk of DNA that corrects whatever defect has been there.

One of the challenges with a lentiviral gene therapy is you're inserting that gene into just a random place in the genome. So it's not in the place where the actual gene lives in reality. So things like promoters and things that modify expression of the gene you lose.

So that works really well for things where you don't need really tight control of the gene. But if you need something that has to be tightly controlled, so for example, hyper-IgM syndrome with CD40 ligand, you have to have very close regulation of that gene. If you have too much, you get disease.

If you have too little, you get disease. It has to be just right. So technologies like CRISPR is actually editing the gene in place.

And for things like CD40 ligand, that's better because you're keeping it with all the right promoters and modifiers, so the expression is still well controlled. The challenge with CRISPR is there's that double-stranded DNA break, which can result in changes in the genome in other places. So there is an issue where you might end up making a double-stranded DNA break

somewhere else in the genome and getting chromosomal abnormalities, or if you get that in a proto-oncogene, you could potentially get a cancer.

So that is a concern that we have with CRISPR. There are new technologies coming out. So one of them is, and they're all based essentially on CRISPR, is base editing, which is one of the things that I've been working with.

And with base editing, we're adding on an enzyme to the CRISPR backbone. We only make a single-stranded double break in the DNA. So the risk of things like disrupting the genome other places is lower.

Base editing is really good to fix one letter, so one nucleotide. So if you've got a point mutation, you can take base editing and go in there and just fix that one letter. The exciting thing with base editing is when you compare it to CRISPR, it's actually more efficient.

So with CRISPR, if you get 60% editing in the cells, you're doing pretty good. With the base editing, we're seeing closer to 80-90%. And also it's more precise.

So we don't have to worry about it making changes other places. The next technology coming along is prime editing. And that one actually has made it to clinical trial.

So that was exciting in that it's been developed for P47CGD, autosomal recessive CGD. A lot of the patients have the same small deletion. Prime editing is a bit similar to base editing, but you can fix a bigger hunk of DNA.

So it's not just one letter that you're fixing. You can fix a bigger place. So for a small deletion, for example, prime editing can go in there and fix that little deletion.

There was a clinical trial by Prime Medicine for CGD for the P47 that was open. And the first patient that was treated was actually a patient from BC treated in Montreal. So the exciting part about that one was that it was approved by Health Canada before it went through the FDA and done in Canada.

So that prime editing, I think, is going to come and probably replace CRISPR in a lot of cases. There's even newer technologies that are more powerful that are coming. So this field is just exploding with technology.

It's really quite remarkable.

Dr. Mariam Hanna:
That is crazy. And like that was the TikTok version of it. OK.

You kind of touched this already, but let's just reconfirm here. Practical distinction between adding a functional copy of a gene versus correcting a mutation of a gene.

Dr. Nicola Wright
So if you insert just the whole gene, you can treat every single patient with that disease. OK. Whereas with things like base editing, for example, that only works for one mutation.

So like with our CD3 delta skin, for example, it's a founder variant in the low germ and meninite population. So everybody has the same variant. So it's powerful for that.

But most other diseases, like CD40 ligand, for example, there's multiple different places in the gene that can be disrupted to cause the disease. So base editing is not going to work as well unless you make base editing for every single individual patient that has an editable variant. But that would be a lot of work and a lot of investment.

So doing something like the lentivirus that can treat more patients, that's the advantage of that.

Dr. Mariam Hanna:
Scalability.

Dr. Nicola Wright
OK.

Dr. Mariam Hanna:
And then let's look at outcomes kind of specifically with these different therapies in terms of immune reconstitution. You've already kind of compared this to where stem cell transplantation in terms of recovery. But what about immune reconstitution?

I think, again, the ADA SCID cohort is probably our biggest.

Dr. Nicola Wright
The cohort that's also been followed the longest. And as I mentioned in those patients, in the ones that have been treated with the lentiviral therapy, over 90 percent of them have good immunoconstitution afterwards. There have been a few patients who haven't had good immunoconstitution, and those patients have gone to bone marrow transplants.

So that is an option if the gene therapy fails, is you can then go back to our traditional therapy and do transplants. But the vast, vast majority of those patients have done extremely well. Some of them do have some lower T cell numbers, for example, but most of them it's not clinically causing them a lot of problems.

Some of the other diseases have been a little bit trickier. With Scott-Aldrich syndrome, for example, there is gene therapy for that. That's a tougher disease because it's not just a T cell defect.

There are things that go along with it, like autoinflammation and things. So those patients, their outcomes haven't been quite as strong as in the SCID population. Chronic rhinitis disease, there's also been some challenges getting enough corrected cells, some of the inflammation and things that they get.

Sometimes that can be a problem with those patients as well. So some of the diseases still need some work to really optimize it. But even so, some of those patients, for example, with Scott-Aldrich and CGD, some of those patients are really sick.

So getting them through a bone marrow transplant is extremely challenging, whereas the gene therapy is less toxic. So even if you might not get the same result at the end, for that patient who is really sick, you may actually get a better result than you would with a bone marrow transplant. So as you can see, there's a lot of nuance with a lot of this.

Dr. Mariam Hanna:
There is. There is. Okay.

If you don't mind me asking, because of the newness of this, when you say like long-term survival, what does long-term survival mean with these?

Dr. Nicola Wright
So there's like a few patients who are out 20 years with some of the early therapies, but the vast majority, we're talking like two to five-year outcomes. So we don't truly have long-term. And I think that is one of the questions we have with these gene therapies is will those, the engraftment, like for example, with the lentivirus, when you insert that gene, will that last for 40, 50 years for those patients?

We don't know. So we're going to have, we would have to try and follow those patients.

Dr. Mariam Hanna:
Okay. If you're counseling a family today, how do you frame gene therapy versus transplant? What does the bedside discussion look like?

Dr. Nicola Wright
Great question. Again, there's lots of nuance there. So part of it is, is there a gene therapy available for that patient's disease or not and where in the pipeline it might be?

And then what does that disease trajectory look like? So again, ADA-deficient SCID is probably the one where there's a therapy available. There's clinical trials.

So and then the other piece with ADA-deficient SCID is you can maintain most of those patients on enzyme replacement therapy. So you have some time. So for those patients, we would counsel, okay, can we get you into a clinical trial?

It's not available commercially. None of these are available commercially. Is there a clinical trial that you're eligible for?

How long will it take you to get into that trial? And can you wait that long for that patient? The other things that go into it, so most of the trials, if you have a matched sibling donor and you need a transplant or a definitive therapy, most of the trials exclude patients with matched sibling donors.

So that kind of bumps you into the transplant route. If you don't have a matched sibling donor, then you may be eligible for trial. And then if there is a trial available, we would start talking to the principal investigators of those trials and seeing if we could get our kids in.

If you have a disease that you might have some time to wait, then we would have a discussion with the family about, okay, so this might be something that will be coming down the line. And we could potentially wait and try and optimize your supportive care and see how things go versus going to transplant. And that, I think, is a very individualized decision with a family.

And it's a little bit different for every patient, I think. I think one of the challenges is there really only are a few clinical trials for different gene therapies available right now. So for the vast majority of patients, it's either you got to stick with traditional therapy, transplant, supportive care.

And they often don't have time to wait for some new gene therapy trial to come up, unfortunately.

Dr. Mariam Hanna:
Yeah, I mean, that's the challenge of these new types of therapies.

Dr. Nicola Wright
We have a few things in the pipeline that I'm hoping we can get into clinical practice in the next five years. And as we get that going, I sort of describe it, we're kind of developing the runway and trying to fly the plane at the same time.

Dr. Mariam Hanna:
That's how the healthcare system functions all the time, actually. Okay. And now let's talk about practical problems like scalability, manufacturing, cost, all these.

So is this something, first off, for the foreseeable future, is going to remain centralized into major centers?

Dr. Nicola Wright
Yeah. So I think in the gene therapy world, as I mentioned, the science is there. We can do this.

We know how to do this. Our problem is that once it's developed, and some of these things have already been through clinical trials, we call the next phase the valley of death. So you get these things going.

The ADA deficient skid is a great example. So it's gone through clinical trials. So they've treated like 100 patients.

They tried to get it commercialized. It was picked up by a pharmaceutical company. And the vast majority of these gene therapies, the ones who have actually gone through clinical trials and shown this works, it's safe, it's a good therapy, have tried to commercialize it.

But most of these are kind of ultra-rare disorders. And the pharmaceutical companies, because the expense is huge, have ended up looking at it and saying, it's not worth it. It's not profitable.

So they've dropped it. The problems with it are, first of all, to develop one of these therapies for a disease, the investment for the development is around $10 million. Initially, the timeline was like 10 years.

That's shortening. And I think the cost is going to start shortening. So that'll improve.

But once you start getting into a commercialized production, like the lentivirals, for example, one of the disadvantages of that is producing those lentivirals in a commercialized manufacturing facility is extremely expensive. And that's where the companies look at it. And they're like, we just can't do this and make any money off this.

So it's very expensive. So we need to figure out how to make it cheaper. We need to get over this valley of death.

And we need to be creative about it. And we need to get people like the government and academic institutions on board. We want to actually just be able to collect the cells from their local center and then ship them to the place to get fixed, and then ship them back to the local center so that we're moving cells instead of patients.

And that'll make things a bit easier. But we have a long runway to pave for that piece, for the access.

Dr. Mariam Hanna:
But you've already started to identify where the barriers are, ways to work around it. That's why we need people like you in this kind of field. Okay.

Shipping the cells rather than the patient. That sounds a lot like CAR T-cell therapy.

Dr. Nicola Wright
Yes.

Dr. Mariam Hanna:
Yes. So let's talk about that. Where does CAR T-cell therapy fit in the world of IEI conversations, or is there a place for it?

Dr. Nicola Wright
I think there's definitely a place for it. This is one of these therapies where it was developed essentially for cancer. So what you're doing is you're taking donor T-cells and you're modifying them using some of the same technologies that we're using for gene editing.

So you take those T-cells and you're essentially using technologies like gene editing, lentiviruses to infect the cells to program those T-cells to target a specific antigen. So for example, in autoimmune diseases, which some of them are sort of monogenetic immune disorders, I think that that spectrum of immune deficiency kind of starts going into your auto-inflammatory, autoimmune things. There is actually a Canadian trial that is just getting put together of using CD19 CAR T-cells, so CAR T-cells against B-cells, for patients with refractory autoimmune disease.

So in those patients, they make a lot of antibody-mediated they're attacking their own tissues with their own antibodies. So if you get rid of their B-cells, they'll stop doing that, and that can significantly improve their disease. And there's been some trials with that in other countries, but we're now trying to bring that to Canada.

So I think we will see those CAR T-cells anywhere where you have a cell you want to get rid of, you can program a CAR T-cell to go in and do that. One of my mottos is T-cells are the bomb.

Dr. Mariam Hanna:
They're pretty amazing. I'm thinking of so many. They're the bomb.

Dr. Nicola Wright
They're the bomb. T-cells are the bomb. They're so important.

But to think that you can infuse a patient with these programmed T-cells, like a few million or so of them, and they can go in and kill your cancer. How powerful is that? Genius.

Yeah, it's kind of amazing.

Dr. Mariam Hanna:
It is amazing. Okay, CAR T-cell, gene therapy, like all these things, what does lifelong follow-up look like for these patients? What does that runway look like?

Dr. Nicola Wright
So I think one thing that's super important is when we're doing these things, most of the follow-up for two years. But on the clinical trials, and the FDA requires this, I'm sure Health

Canada probably will too, that there be a second follow-up study for a minimum of 15 years. Because we don't know what happens with these patients 30, 40 years from now, we need to make a huge effort to see those patients and keep seeing them annually so we can see what happens over time.

So that's really important. And I think that's also what that's going to require investments. Doing any long-term studies, as we know, is very challenging.

So we're going to need to get that funded and have support to see those patients. Our bone marrow transplant patients also get long-term follow-up once a year, so it's not that much different. I think the difference will be with bone marrow transplant patients with the chemotherapy they get, we have to watch for long-term toxicities of that chemotherapy.

Whereas with the gene therapies, we're not going to have to watch for so much of the chemotherapy long-term toxicities. But we're going to have to watch what's their long-term immunoconstitution. We can monitor and see how much of the either edited cells are still present in their blood, how much of the lentiviral is still in DNA is incorporated into their cells.

So we can monitor that over time. And I think we're really going to need to do that over time to see if there's any issues that start cropping up later on. But for what the child looks like, if everything goes well with the gene therapy, you end up with a patient who has essentially a normal quality of life, can go out and do whatever they want to do.

They just have to come to see one of us and get some blood work done once a year. That doesn't sound so bad.

Dr. Mariam Hanna:
No. No. All right.

Perfect. Time to wrap up and ask today's immunologist, Dr. Nicola Wright, for her top three key messages to impart to patients and physicians on today's topic, gene therapy and IEI. Dr. Wright, over to you.

Dr. Nicola Wright
So I think the first key message would be that gene therapy is a very promising treatment for patients with IEIs. And the technology is moving very rapidly. And it is something to definitely consider that we're all going to have to keep on top of where things are at for our patients.

I think my second key point is there is a lot of work to do with regards to access and sorting out how do we get patients access to these therapies and how do we get them into clinical trials faster? How do we manage those problems? My third key point is something that we haven't actually touched on yet is the science fiction.

Seems like science fiction, but it's coming very quickly is all of these gene therapies are going to be turned into in vivo soon. So there's lots of technology coming there where, for example, these base editors and prime editors, you can package in a little lipid nanoparticle and then we'll be able to actually inject those into patients. So the future is one IV infusion, likely no chemotherapy, and that'll cure our IEIs.

Dr. Mariam Hanna:
Mic drop. Wow.

Dr. Nicola Wright
Very cool.

Dr. Mariam Hanna:
Thank you, Dr. Wright. That is actually an episode in and of itself. Yes.

So stay tuned for part two. Thank you, Dr. Wright, for joining us on today's episode of The Allergist. Thanks so much for having me.

For show notes and relevant links from today's discussion, visit CSACI.ca. While you're there, check out the Find an Allergist tool to connect with a specialist near you. If you enjoyed this episode, we'd love your support. Subscribe wherever you get your podcasts.

Leave a review and a five-star rating. It helps others find the show. And remember, though it may seem like the valley of death, I shall have no fear.

Thanks for listening. Sincerely, The Allergist.