Ruth Adewuya, M...: Welcome to Stanford Medcast, the podcast from Stanford CME that brings you the latest insights from the world's leading physicians and scientists. If you're joining us for the first time, be sure to subscribe on Apple Podcasts, Amazon Music, Spotify, or YouTube, to stay updated with our newest episodes. I am your host, Dr. Ruth Adewuya. Today, I am joined by Dr. Crystal Mackall. Dr. Crystal Mackall is the Ernest and Amelia Gallo Family Professor at Stanford University, founding director of the Stanford Center for Cancer Cell Therapy, leader of the Cancer Immunology and Immunotherapy program, and director of the Parker Institute for Cancer Immunotherapy. Dr. Mackall's 27-year tenure at the National Cancer Institute and her subsequent work at Stanford have significantly advanced immunoncology. Her work has advanced our understanding of fundamental immunology, and translated this understanding into treating human disease, with a major focus on children's cancers.

Her team was among the first to demonstrate the effectiveness of CD19 CAR T-cells in pediatric leukemia, and developed the CD22 CAR, which received breakthrough therapy designation from the FDA for pediatric and adult malignancies, and is undergoing potentially pivotal testing. She's leading the work with GD2 CARs for pediatric brain tumors, and developing new platforms to enhance CAR T-cell therapy for solid cancers. She has published over 250 manuscripts, is a member of the National Academy of Medicine, and has been recognized with numerous awards. September is Childhood Cancer Awareness Month, a time to raise awareness of pediatric cancer and those who have battled the disease. I'm so grateful to have Dr. Mackall here with us today. Thank you so much for being here.

Crystal Mackall...: Absolutely, Ruth. Thank you so much for having me, and I do want to say heartfelt thanks to Medcast for wanting to highlight the issue of childhood cancer.

Ruth Adewuya, M...: Could you start by sharing a little bit about your journey into the field of pediatric oncology, and what inspired you to focus on childhood cancer research?

Crystal Mackall...: It's one of those things which I hope during the course of the hour it will become clear why raising awareness of the challenges that this field still faces is really important, because without awareness and prioritization of the resources that are needed to make progress here, it's not going to happen. So I really am thankful that we are taking the time talking about our children who fall prey to this emperor of all maladies, one of the scariest diseases for mankind.

So my journey, I was born and raised in Ohio, a working-class family. I always knew that I wanted to be a doctor, and so I went to the medical school down the road. The medical school's name was Northeastern Ohio University's College of Medicine. I was a doctor long before I was a scientist. I knew very early that oncology pulled me like a magnet. Why? In some ways, the same today, it was the worst disease, patients suffered, it wasn't just the patient, it was the family, they needed your help, they needed your emotional support, and scientifically, we needed to do so much work, I saw it as such a challenge. And so, I knew I was going to be an oncologist, but I didn't know if I wanted to do adult or

pediatric oncology. I did a combined internal medicine pediatrics residency, and it gave me a chance to see the state of the field.

So this is now the '80s, and at that time, the treatment of pediatric cancers was much more advanced than the treatment of adult cancers. We were giving many drugs to children, so-called multimodal therapy, and we had cure rates that were 60% to 70%, and the chemotherapy was making a big impact. On the adult side, however, there wasn't much the medical oncologist had to offer. The reason I chose pediatric oncology is I felt so much more optimistic about what we were offering and the opportunity for progress. That was 1989 when I made that decision.

This point of awareness is if you fast-forward 30 years, 35 years, it's crazy what's happened, because adult oncology, the progress has dramatically accelerated since that time. We treat cancer today so much differently in the adult patient population than we did back then, and it's great. It's really a clear proof of principle that the recipe for how we did this works. But children's cancer has stalled, we are still treating kids with cancer the way we treated them in the 1980s. Now, think about the 1980s, there wasn't any internet, there weren't cell phones. Technology has just accelerated dramatically, but it hasn't trickled down to children's cancer.

Ruth Adewuya, M...: There's so much to unpack there. First of all, just your journey and the process of you identifying your specific passion and what area that you would focus on in medicine. I resonate so much with the idea of I always wanted to be become a doctor, and yes, I became a doctor type thing. But also, just what you said about the leaps and bounds in adult medicine, and the fact that we are still treating children as we did in the '80s. It's hard for me to think of one innovation that we haven't improved upon since the '80s, and somehow-

Crystal Mackall...: Ruth, it's a really good question. I can't think of one either.

Ruth Adewuya, M...: Yeah.

Crystal Mackall...: We still do surgery, maybe now we use a robotic. Radiation has changed dramatically. I don't know, you're right.

Ruth Adewuya, M...: Yeah.

Crystal Mackall...: And there's so much to unpack there. Some of it's biology, some of it is bad luck, but some of it is also the way that medical progress is made and how that has left out children with cancer.

Ruth Adewuya, M...: Absolutely, and I'm sure we'll get to it. You already set the stage that we're not where we want to be in terms of pediatric cancer, but let's talk about the current state of pediatric cancer. What are the most common types? How do they generally differ from adult cancers?

Crystal Mackall...: The most common cancer in children is leukemia, which is different than adults. The second most common are brain tumors, which is not that dissimilar from adults. And then, the third most common would be solid tumors.

Now, the way cancer develops in a child is very different than the way it does in adults. In adults, what we've learned is that the development of cancer takes place over a long period. It's usually the result of a sum total of genetic events, many of which could be imposed by lifestyle or exposure to toxins of some kind, whether it be cigarette smoke or the sun or chemicals in our system. Children's cancers, however, tend to be more developmental mistakes, and they don't tend to grow slowly over years and years, they tend to result from maybe one genetic error, maybe two. Think of it like a switch, the children have a normal cell one day, and the next day, the wrong mistake happened in the wrong cell at the wrong time, and voila, you now have this really aggressive tumor.

Another point to make about children's cancers is children's bodies are full of stem cells, that's why they heal so well. They need the stem cells to get them through their long lives, that's how our tissues are replenished. But it's those stem cells that largely give rise to the cancer. When they do turn cancerous, they can be uber aggressive. The pace at which a children's cancer grows typically much faster than that of an adult cancer, and so that gets to why chemotherapy worked quite well in children's cancers.

Chemotherapy isn't a very smart treatment, it goes after cells that are dividing, and because children's cancers have such a high rate of proliferation, we started giving chemotherapy in the '60s. This was all a byproduct, pretty much, of World War II, and the use of poisons in World War II, that's where chemotherapy started, crude. You did it in a way that you tried to kill the tumor and not kill the patient, and the thing is children's bodies could tolerate it. So these were the two reasons why chemotherapy really worked in kids much better than it did adults. The tumors were proliferating more rapidly, and the children's bodies could handle the insult.

And we've gotten very far with chemotherapy. Currently, 80% of children's cancers are cured. When I say the glass isn't half full, I think it's half empty, but somebody could look at it and say, "Crystal, the glass is half full. Come on, 80% cure rates, what's so bad about that?" What's so bad is one out of five aren't cured, so it's still the single largest killer of children due to disease. But the real, real bit is that these chemotherapies, even though the patient can survive it, they survive it with long-term damage. They are trading their cancer for other diseases. They may be cured of their cancer, but they are not likely to live a long healthy life. And keep in mind the reason they got cancer in the first place, many of them also come in with some genetic predisposition, which also increases their chance of problems, so there's always a complexity there. We use chemotherapy a lot in kids, it does work, but the price we pay.

Ruth Adewuya, M...: And I think that is the push and the impetus to look for alternative methods of treatment, that's the reason to push beyond the 80% that you were talking, why look at other options, this is why.

Crystal Mackall...: Yeah. And I think talking about the late effects of cancer in children, it wasn't until we started looking at late effects in the '90s that we said, "Oh my goodness, look at these kids." We say they're survivors, and they are, but we see things like second malignancies. I would say 10%, 20%, in some cases, 30% of the kids will get another cancer. We see things like brain damage. In medulloblastoma, the most common brain tumor of childhood, yes, there is a 70% cure rate, but of those 70% of those kids who are cured, less than one third of them are able to live independently as adults because of the brain damage induced by the treatment. Those are some examples. We see hormonal problems. Many of these kids can't go on to have children, bear children of their own, father or mother children through typical means. We've got brittle bones, we've got premature aging. You name it, these kids, they've got it. So we can do better, there's no question in my mind, we can do better with what modern medicine can offer, it hasn't been done.

Ruth Adewuya, M...: Yeah. What I'm hearing from you as well is challenge that comes as a clinician when you are treating your patients knowing this, what are some of these challenges that you encounter when you are diagnosing and treating pediatric cancers? And then, I might even tack on the second part to that, how do they influence the treatment protocols that you offer?

Crystal Mackall...: Absolutely. So let me just talk about the status quo. Pediatric oncologists are masters at treating toxicities. Nearly all the children will have blood counts that drop, and so they have to get blood transfusions, or platelet transfusions, or be treated for infections. We often see problems with nausea and vomiting, liver toxicity, kidney toxicity, et cetera. So that's what modern pediatric oncologists spend most of their time doing is preventing and treating toxicities. What I want to get across is that the status quo, it's as good as we have right now, but we shouldn't be satisfied with it.

There is an immense understanding, the culture of pediatric cancer medicine is one of understanding that you are treating not just the patient but the whole family, and that you are treating this child not just for today but trying to get them through this experience intact, things like child life, pediatric hospitals are in tune to what it takes to get a child through the treatment emotionally intact and not psychologically scarred. And so, that's what a pediatric cancer ward is all about is delivering the therapy safely, but also doing it in a way that minimizes the fear and the pain and the suffering. Given the tools we have, the community does an amazing job of delivering compassionate and safe care to children. We rarely lose a child due to toxicity because the oncologists are really good at what they do.

Ruth Adewuya, M...: I will say that to your point about the oncologist is like the orchestra conductor-

Crystal Mackall...: Absolutely.

Ruth Adewuya, M...: ... trying to manage all of these different aspects that go into caring for a child with what is available, and that is just incredible and challenging work, it's just amazing, and even the hospitals that are basically changing spaces, to ensure that the environment in which children are going through this difficult moments-

Crystal Mackall...: Look at Lucile Packard Children's Hospital, you walk through there and it is a happy place, there are so many special touches to make the children and the families feel at home.

And the other point that you touched on is the oncologist may be the orchestra conductor, but they are only one member of an essential team, and the team includes the nurses, the bedside nurses, the nurse practitioners who often see the children in clinic and develop these amazing relationships with the children and family, build all that trust, the social workers, the child life, the psychology support, the physical therapist, the occupational therapist. In pediatrics, one of the great things is that nearly all children are treated at specialized centers, and for that reason, our outcomes associated with access to care, they're better than they are in the adult community. I do believe that in the developed world, that children, regardless of their socioeconomic status, are largely getting the optimal care.

Now, that said, the truth is, because most children with cancer historically have been Caucasian in the United States, the treatments have evolved based on what is best for Caucasians, because they make up the most of the research studies that have led to our treatment standards now. And we know that, for instance, Latino patients, they are not doing as well in terms of children's leukemia. It's also true for African American children, but most notably for the Latino population. It may be that the disease is a little different, it may be that the patients don't tolerate the chemo as well. We don't know exactly why it is, but I do think that we have some problems with equitable care. But in general, most children are being treated at centers that really know how to deliver all of the multimodal care that's necessary.

Ruth Adewuya, M...: I think that's a very important point to let our listeners know. I think it's also a great segue into the conversation around opportunities and research, and curious how these clinical experiences and these things that you've noticed, such as access and the differences between Latinos and African Americans, how have these clinical experiences shaped your research focus? I'm curious to hear your thoughts on that.

Crystal Mackall...: So of course, somebody like me who is a researcher at heart, what I am looking at all of the time is how can we do better, how can we change the way we're treating in 10 years? You accept the status quo today and you deliver the best possible care you can in the most compassionate way, as a researcher, this is my job is to be thinking about 10 years from now, how should we be doing this? Ever since I started my career, I've been thinking about that.

And in the '90s and in the 2000s, in adult cancer medicine, there was a revolution that was related to understanding the genes that drive the cancer, and drugs were created that were specific to the tumor. These were drugs that went after the mutated genes. So this was a revolution. These were smart therapies, they were going after the specific mutation, it was a pill they'd take every day. Try as we might to use these pills that were developed by pharma for pediatric cancers, they just largely didn't work. So if the small molecules that go after the mutant kinases

aren't going to work in pediatric cancer, what else? And this is where immunotherapy has really entered center stage.

Immunotherapy in pediatric cancers has shown some really exciting signals, maybe even suggesting it might even be better in pediatric cancers than adult cancer. We have had half a dozen approvals in pediatric cancers, which is really amazing. These immunotherapies are going after the cell like a magic bullet, where they say, "This cell looks different than this cell, and I've been trained to find this cell." And we've got an antibody that's shown activity in the most common solid tumor of childhood, we've got an antibody that's conjugated to another antibody that's shown activity in ALL, leukemia, and then we had the CAR T-cell that had activity in childhood leukemia.

And this was so exciting, because it was, for the first time, this was a new class of drugs and the first FDA approval was for children. We had a literal poster child, Emily Whitehead, who was treated at Penn, I was at the NCI at the time, and Penn and my group were racing to get the first CAR T into kids, and that's great, the healthiest race in the world, when Emily was treated, and word traveled fast, that this is really something.

And so, we were excited. At that point, this was around 2011, we really thought, now it's going to change, we're going to have immunotherapies and CAR T-cells, and they're going to change the way we treat children's cancers. And they have dramatically impacted outcomes for children with this particular common type of leukemia, so that's a win, we've got to take our wins. The problem is that's all we have in terms of an approved drug, and this is where I'm filled with this conflict, incredible excitement for what can happen scientifically, the progress has been immense, and then this frustration of, but how are we going to develop the drug? Who's going to take the drugs from the children's hospital that did the exciting early trial? We don't have anybody to hand it off. Or we do hand these things off, oftentimes perhaps naively, and the company doesn't do anything with it, it puts it on the shelf.

Ruth Adewuya, M...: And why is that? Why is there no one to hand it off to?

Crystal Mackall...: Yeah, this is what I've spent lots and lots of hours trying to understand, and your first reaction is anger. The reasons they don't develop these drugs are many and varied. One might be that they have other priorities in their pipeline. One might be that there's concern about toxicity. One might be that they don't think the data's strong enough. And all of that might be true for any particular drug, but when you look over time at the pattern, what you come to understand very clearly is that it's a decision made to maximize return on investment for their shareholders.

And I will tell you, Ruth, I used to get angry about this, I co-founded four biotech companies and I've really dug into biotech wanting to understand how to commercialize things. But at the beginning, I thought they'll do the right thing, even if they have to carve out a little bit of funding, they have other ways of maximizing their return. No, the truth is it's hard for a biotech company to make it, it really is, and in order to make it, their belief is they have to be as lean and

focused as possible. There have been laws, the RACE for Kids Act passed, written by a good friend of mine, Nancy Goodman, who lost her child to medulloblastoma, and couldn't believe, when she went through this in 2012, that the drugs looked like from the 1980s, and she's passed laws to try to both incentivize drug development by biopharma and require.

Ruth, they haven't worked. They have improved the situation, but they haven't solved the problem. We need different business models, and in that business model, it's not all about maximizing return on investment for shareholders, society needs to be a part of the solution, and then, of course, hopefully philanthropy. So we have to be more creative, and this is going to take some effort and time.

Ruth Adewuya, M...: It's almost like we need to go into a GoFundMe model for it.

Crystal Mackall...: No, we do. And I don't know, is it that, or is it that we need a congressional earmark?

Ruth Adewuya, M...: Yeah, probably.

Crystal Mackall...: Both.

Ruth Adewuya, M...: You have served in a lot of leadership roles in a variety of different cancer therapy-related organizations, and just another way to understand how these experiences have also shaped your perspective on the complexities of pediatric cancer, and how this has given you another lens around developing new treatment modalities.

Crystal Mackall...: Absolutely, Ruth, and the thing about every pediatric oncologist that I know of, of course they're physicians at heart, most of their day is focused on understanding how to deliver the best therapy, the safest, but the other thing is that each and every one of us are advocates. Advocacy is just part of being a pediatric oncologist, and probably a pediatrician in general. Just by the fact that pediatric cancer is rare compared to adult disease, we need to advocate for public monies and for access to grants and all of that because it's the right thing to do.

But it's not just that, children's cancers are extremely, what I want to say, fundamental. In other words, every single thing that we have learned about children's cancers also play out in adult cancers. And so, adult cancers, they're complicated because you've got that whole history that's happening. These cancers have oftentimes hundreds of mutations in them. How do you know which one is important? We have the drivers, we have the passengers, we don't really know which is which. Children's cancers often will have a couple, and those couple are typically the drivers.

Let me give you some examples. P53, that is the most commonly mutated gene in all of cancer. How did we discover P53? We discovered it because children who were born into families that had family syndrome... So if a child gets a cancer, you want to be thinking about is there a genetic problem? Children with P53

mutation develop sarcomas early in life, oftentimes their mother would have breast cancer. You wouldn't know if the mother just got breast cancer because it's common. That was part of something called Li-Fraumeni syndrome that's driven by P53 mutation, and it helped us to understand now the most common gene in all of cancer medicine. We have other examples. The SWI/SNF complex is another very commonly mutated gene set that was really first discovered in a very rare pediatric tumor called malignant rhabdoid tumor.

So there is reason to study children's cancers independent of it's the right thing to do because we learn important things. The ability to give multimodal chemotherapy, first done in children, the first activity of CAR T-cells to the extent was in children's leukemia. So we're now seeing activity of CAR T-cells in pediatric brain tumors, and it's like nothing we have seen in adult brain tumors. So once again, what we learn from studying children is fundamental, and it will help us develop better therapies for adult cancers too.

Ruth Adewuya, M...: One of the things that happens in the public space or in society is that every so often in the news you'll see it picked up around the race for cure for cancer and why there isn't a cure for cancer, or there might be this thing that we're X amount of years away from a cure for cancer. I gather from our conversation there's this huge potential, but how do you envision this evolution, especially for pediatric populations?

Crystal Mackall...: Now, this is a really good question, Ruth, and over the course of my career, I have seen it evolve dramatically. Remember in the '80s, what the country was really facing was the AIDS pandemic, and the AIDS pandemic changed medical research forever, to me, mostly because it was the first time that the public got involved in an advocacy way that they were really conversing, they were giving their opinions to the researchers and to the funders. Before that, it was all very passive. The public said, "That's medical research, that's over there. I hope they find something for my disease." And when ACT UP and all of that history, which is an amazing history, it forever changed the role of advocacy, and that's a great thing. We now have the Coleman Foundation, we've got foundations for children's cancer, we've got foundations for prostate cancer, ovarian, and you name it, and it's a good thing because it has accelerated investment, and it has held funders accountable, and it has held researchers accountable.

On the other hand, there's a flip side there too. A, what if you have a rare disease and you don't happen to have an Elizabeth Comen Foundation for you? You will often fall under the cracks. And yet, the investment is low. So there are downsides to this advocacy. And the other thing that happens is then people start making promises and politicians start making promises. But on the other hand, if you say, "We're going to cure cancer in 15 years," it's not going to happen. Cancer is hundreds of diseases. This is why each of us have to advocate, need to do it in a way that I think you want the public and the public money to believe something can happen, but how do you walk that fine line of not over-promising?

Ruth Adewuya, M...: Exactly. You want there to be hope, but you want it to be realistic hope. We talked earlier and you mentioned the idea of access, but I also wanted to do a deeper dive into it, because as you talk about innovative therapies and how it's

very critical in pediatric oncology, what do you see as some of the main barriers to broader access, especially when you're talking about gene therapies and immunotherapies-

Crystal Mackall...: Yeah, yeah.

Ruth Adewuya, M...: ... and what steps can we take to ensure that these cutting-edge therapies reach more pediatric patients?

Crystal Mackall...: This is where, when you talk about the market failure, the fact that we don't have the innovative new therapies on the market for children's cancer to the extent that we do adult cancers, when you talk about dealing with the market failure for these rare diseases, it's not uncommon for folks to say, "Can't you just have perpetual clinical trials?" I'm going to divert a minute and talk about our brain tumor CAR T efforts, which I think are really exciting and that will be a foray into answering your question.

There are some diseases for which we have made zero, zero, zero progress. One of these is something called diffuse midline gliomas. This is the second most common pediatric brain tumor. It is the largest killer of children due to brain tumors. It typically afflicts kids between the ages of four and eight years of age. They are otherwise well, and then they would maybe show up stumbling a little, or their eyes aren't tracking exactly, and they go to see their doctor, and somebody does a scan of their head, and they see this tumor deep in the brain stem. You can't get at it surgically because it's involving these vital structures. And the treatment today in 2024 is the oncologist walks into the room with the parents and says, "Your child has diffuse midline glioma. We're going to give him or her radiation. His or her symptoms might get a little bit better, that'll last about six weeks, but then the tumor will grow and your child will die. The median survival is about nine months, and there's nothing more we can do."

This is an example of a disease that we can't do better. Michelle Monje is a pediatric neuro-oncologist here at Stanford who'd been studying diffuse midline gliomas. So children, after passing away, their parents would agree to have their brain sent to Stanford, or a portion of their brain. When I arrived at Stanford, she did a very simple experiment. She had these cells in a dish and poured some antibodies on them and said, "What sticks?" And she found that antibodies to this molecule called GD2 stuck very well. This turns out GD2 was a well-known molecule. She knocks on my door and says, "Crystal, don't you make CAR T-cells to GD2?" So this was 2018, and we saw in mice, which we treated with these CAR T-cells, dramatic benefit, and Michelle had been studying this disease for a decade, treating with various drugs, et cetera, and had never seen anything like this.

We said, "We're going to get a trial done." And so, in two years, we got the trial open, right during COVID, first patient was enrolled in June of 2020, and we've been doing this trial since that time, and we are seeing some really exciting results. I'd say it's not a home run, but we're on base, and in this disease, being on base is really exciting because we don't have therapies. We have one patient who is now over three years out, there is no tumor, his symptoms have largely

resolved. He was unable to walk hardly at all when he came, and he's now traveling Europe and things like that. We have several patients whose tumors have shrunk very significantly, several patients who've had clinical improvement that's lasted several months.

So what do we do with this? I don't want to give it to a company, because I think they will raise money on it, and then I just can't trust them. So we're trying to use a nonprofit model to get the trial done. But when you talk about it with people, they will say, "Can't you just do clinical trials? Just keep doing clinical trials, just open it up at a bunch of hospitals." The problem with that is it's only the kids whose parents can take off work, come stay for the month, or whatever it takes to get each therapy, you don't have access if you are not able to get these drugs FDA-approved so that they're available at pediatric hospitals across the country and not just in the US, and hopefully in the developing world eventually, by the way. We are getting CAR Ts in the developing world now, India now has several trials of CAR Ts, and I think we could get these there.

But this is to say that this whole market failure is tied up in access. The question is when it becomes an investigational therapy, which is so important in children, it's only a select population who want to be part of a research study and who are able to travel, and there's only so many pediatric hospitals that can have the money, raise the money to do the clinical trial. It costs thousands of dollars to do these. So the market failure and the access problem are really linked.

Ruth Adewuya, M...: First of all, congratulations. It sounds like there's incredible work being done and some positive outcomes already available, and long may continue. There is a call to action researchers and people who are willing to walk alongside to bring this work to life, because there is a need for an alternative model to increase access to these types of medications. As we wrap up this conversation, what are some of your final thoughts or clinical insights that you would like to share to clinicians who are in the same space you are in right now, or upcoming, that are on the front lines of pediatric oncology?

Crystal Mackall...: I think that we should be incredibly proud of the history of our field, we, the proverbial we, have led the way in cancer medicine, really. If you go back to the '60s, we provided the first evidence that you could really cure cancer with these multimodality therapies. I think that pediatric oncologists have led the way in delivering compassionate holistic care to patients and families. We've led the way in understanding the survivorship issues, that it's not just about curing of this disease, doing it in a way where the patient is healthy enough to live a long healthy life after their cancer. In many ways, pediatricians and pediatric oncologists have been the leaders in cancer medicine, and I hope that we can remain in that way. I hope that we don't settle for where we are, and really keep looking to the future for how we can do better for our children.

Ruth Adewuya, M...: Wonderful. What an incredible call to action for all of us. Thank you so much for being here.

Crystal Mackall...: My pleasure.

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