Episode 34 – Travis Young: Finding a cure for cancer with novel immunotherapies

Travis (00:00):

If I wasn't at Calibr, I think I'd be doing YouTube videos... I'd be trying to be the Neil deGrasse Tyson of medicine….

Drew (00:07):

Yeah. Science fiction. But then it's just like, come on guys. We're taking out T-cells and reengineering them. This is science fiction….

Drew (00:17):

Welcome back. And what a privilege it is to be here. My name is Drew Duglan and this can only be Science Changing Life. Today. We join the fight against cancer as I'm joined by Travis Young, from Calibr, the drug discovery and development branch of Scripps Research. Travis leads a team of researchers that have developed a new way of reengineering our own immune T-cells against deadly tumors, which has the potential to revolutionize the field of oncology. So let's jump in and visit Travis as he admits how a passion for chemistry and cancer biology may have been born out of some less than stellar English skills.

Travis (00:54):

Yeah, I, I grew up in New York. I grew up in downstate, New York in a little town called Sayville, Long Island. Grew up on the water spending a lot of time out surfing or, uh, hanging out at the beach. My grandfather worked at Brookhaven National Laboratory. He was the fire marshal there for many, many years. And I remember kind of being interested in what was going on there as a kid, but never really picking it up as, as a passion or never really taking on any additional science classes in high school or anything. But when I went to go to college, I actually enrolled as a, as a computer science major. You know, it was right after the .com bubble. And I was like, oh, you know, this seems to be what, where the jobs will be when I get outta college. And the first year I was sitting there with my roommates at, at lunch and, and they were all doing the, the New York times crossword puzzles and I was doing their organic chemistry homework. And so I realized I could read and write organic chemistry a lot better than I could read and write English. And I said, maybe I should switch majors and go into organic chemistry. And so that's how I got my start in chemistry at Boston college.

Drew (02:04):

Wow. So it seemed like maybe organic chemistry kind of came naturally to you then.

Travis (02:09):

Yeah. Yeah. Or, uh, I'm just terrible at English…

Drew (02:16):

So how did you get involved in, in cancer research? Was that via chemistry or what?

Travis (02:22):

You know, I did my PhD with, with, with Pete Schultz and there were so many projects that you were exposed to. We were working on everything from AMD to, to diabetes and, uh, everything in between. There were oncology programs there as well. And after, after being in Pete's group, I went and did a

postdoc with Chris Walsh at Harvard Medical School. And I did natural products more in the enzymology side of things. And those molecules are generally antimicrobials, but there's some aspect of them that, that has some interesting activity in, in cancer. But when we built Calibr and when I came back to, to build a group in biologics, you know, biologics are very biased towards oncology and it was a space that I always wanted to get into because it's something that touches literally every person we know, right. You, you can't, you can't get away from, from cancer and it, and it impacts everyone in such a huge way. I really enjoy going back through the history of, uh, cancer therapy, Siddhartha Mukherjee has that book cancer, The Emperor of All Maladies. I, I love that, that historical perspective, but it's so frustrating to look back at everything that we've thrown at cancer yet, the problem is just, is still so pervasive.

Drew (03:41):

Right? Yeah. It's such an unmet need. And the topic we're gonna be speaking about today is really cancer immunotherapy. And I think a lot of people, when they think of the immune system, especially after the past couple of years, it's, you know, bacteria viruses keeping those guys out, but it's amazing that the immune system also seems to recognize and clear away cancer. Right?

Travis (04:03):

Right. And, and it's interesting that that concept of the immune system being so integral at keeping cancer at bay has been around for a, a long time - back in the 19th century William B Coley had been treating patients with sarcoma and he came across a patient whose sarcoma had spontaneously regressed after getting a, a streptococcal skin infection. And he went on to dig into literature and find these case studies of, of patients whose tumors would disappear after infections. And he came up with a cocktail of bacteria that he was injecting into his patients called Coley's toxins. And it was actually working. It worked really well. Well, I say it worked well. He was able to, to get really impressive responses from several hundred people or so, but the studies were not really controlled. So you couldn't really understand how well it was working.

Travis (05:02):

And at the time radiation was becoming the favored method of treating cancer. And so that really took hold, uh, in the medical community and, and his work was really just dismissed for, for many, many years. And then after World War I, mustard gases became appreciated done on how they could be used for as a, as a set of toxic chemo. And so his work was, was kind of ignored for a long time. And we've had this renaissance in the last 30 years of understanding how to use the immune system to fight cancer. And it's become appreciated. Now that cancer is just as much of a disease of the immune system's inability to recognize a malignant transform cell as it is a disease of the cell itself becoming malignant.

Drew (05:47):

Wow. That's amazing. I never actually thought of that - that sort of the advent of radiotherapy and chemotherapy sort of kept the immunotherapy possibilities in the shadows.

Travis (05:58):

Yeah. Yeah. And so traditionally people talk about that in terms of pillars of cancer therapy and there's four or five pillars of cancer therapy. Surgery was the first pillar of cancer therapy around the turn of the last century. That was all they could do is radical resections of the tumor in any mass that was around in a tissue that was around it to try to keep any type of metastasis at bay. And then, you know, radiation came in vogue around that time and then chemotherapy. And then the fourth pillar, sometimes people

consider as targeted chemotherapies, more modern approaches towards inactivating specific enzymes or pathways within, within a cancer cell. And then immunotherapy has become that fourth or fifth pillar. It wasn't really appreciated that it had such a significant effect for so long, at least not broadly in the community.

Drew (06:47):

Right. And that William B Coley story is just so interesting that that observation happened way back then. And so would I be right in thinking that the bacteria he was injecting into his patients was sort of activating the immune system and then that immune activation was then taking care of some of the cancer.

Travis (07:06):

Yeah, that's right. It was an adjuvant; he was a nonspecific adjuvant. And when the immune system was ramping up, it was then, uh, tackling the cancer as somewhat collateral damage to immune cell activation.

Drew (07:18):

Wow. Fascinating. And so fast forward to now, and when we say immunotherapies now for cancer, what are some of the types we're talking about?

Travis (07:29):

Yeah. A good, good question. So in one of the first, I guess you could categorize this somewhat, somewhat broadly into things that activate the immune response. So immune agonists like Coley's toxins or interleukin 2 is one of the first immunotherapies that was approved back in I think the nineties. There's vaccine based approaches, which people are obviously very familiar now with COVID, but the vaccines to try to prevent or try to treat cancers have been tried for for many, many years. The best example of a, of a preventative cancer vaccine is Gardasil, which prevents HPV infection, which HPV can lead to cancer. But probably the, the most, uh, effective or the biggest immunotherapies that are out there are checkpoint blockade inhibitors. And these are monoclonal antibodies, which target the brakes of the immune system. And when we block the brakes, we release the immune system's ability to then recognize cancer cells as foreign until as far, and to eliminate them.

Travis (08:27):

And then more recently, uh, cellular immunotherapies have been approved. And, um, what I'm working on in my lab is, is chimeric antigen receptor T cells or CAR T-cells. And those were actually the first approved gene therapy in the United States. I think what all of these things have in common is how durable the responses are that patients have. So they don't work in every patient, but when they do work, the amount of time that the patient spends in a complete response. So in other words, how long it takes for the, uh, the cancer to come back is many, many years, or sometimes never. And that's very different from chemotherapy where it's just debulking or knocking down the tumor, but eventually the tumor will gain resistance to come back. When you activate the immune system, the immune system in the patient is still there. Well, after you're activating it. And so the immune system can stay and survey the body for any residual cancer cells for many, many, many years. And I think that's, that's, what's really exciting is, is how, how durable these responses can be in patients.

Drew (09:32):

Got it. Yeah. They've been such a game changer and obviously that relapse for the cancer patient is their absolute worst nightmare after going through everything the first time. And so one of the main areas of, uh, immunotherapy is the CAR T-cell therapy, which I know you and the folks at Calibr are working on. So how does that line of therapy work?

Travis (09:54):

It's a gene therapy and a cellular therapy. So what we do is patient comes in, they, they sit down in a chair, they undergo a process called leukapheresis, which is where we take out T-cells and white blood cells concentrate them down into a bag. We ship that bag to a cell manufacturing facility, and then we engineer the cells with a lentiviral vector, which is interestingly derived from HIV. And that vector harbors a gene, which allows the T cells to find and eliminate cancer cells within the patient. So when we're done manufacturing the product, we freeze it down, we ship it back to the hospital site and that's where it gets infused into the patient. And then the cells they're autonomous, they work on their own, they go and, and via seek and destroy method, eliminate cancer cells, wherever they are in the body.

Drew (10:44):

Wow. That's amazing. So you're just kind of changing the molecular things on the outside of these cells to now recognize the cancer?

Travis (10:52):

Right. You're programming a patient's own cells to be able to recognize their own tumor.

Drew (10:57):

Wow. So how much blood do you need from the patient to do this? And then when you put the T cells back in what happens to the rest of the T cells in the body?

Travis (11:06):

Yeah. Good, good question. So when we do the leukapheresis, it's concentrating down the white blood cells out of the blood. And so we take out, I think about 400 milliliters, but it's a concentrated solution of, of cells. So the patient's plasma is returned back into them. So it's not a very large amount of fluid; for a comparison, a unit of blood that someone might go and donate is around 500 milliliters. So we're taking it just about a unit or under a unit, not, not very much blood. And when we go to give those cells back into the patient, the patient receives a preconditioning chemotherapy and that depletes their endogenous, uh, levels of, of immune cells in order to make room for these new immune cells to grow and proliferate and, and find an attack tumor cells.

Drew (11:57):

While car T-cell therapy has had some major successes, such an intense immune response can come with some significant collateral damage. This prompted Travis and the team to develop a more finely tuned approach to CAR T-cells, which gives them all of the tumor attacking power of earlier methods. But with more precise dosing and less off target effects.

Travis (12:19):

The story that many people are familiar with is the story of Emily Whitehead. And she was a, a young girl at UPenn (University of Pennsylvania) who, uh, had received multiple other lines of prior therapies for ALL leukemia. None of them had worked for her. Her parents were, were down to their last option, which was to find a clinical trial for her to enroll in. And they found a trial at Penn and she went in, received the cells and she had a complete response, no tumor left in her, in her body and is still doing well to, to this day, I think almost 10 years later. So really incredible story, but she had a really severe reaction to the cells as well, because it, when you put a T-cell in, uh, T-cell is immune cell. If it finds a big bulk of tumor cells, it's going to react to those tumors, uh, cells as if they were foreign.

Travis (13:10):

And so that's a huge immune reaction in the body. And patients can get very sick in something called cytokine release syndrome or, or patients have died, um, because it causes, uh, brain swelling as well. And cerebral edema is a really big problem. And so we saw this incredible efficacy and the opportunity for potentially a curative response. And then we saw these terrible side effects, which were, in some cases, patients were, were passing away from them. And we said, how can we marry something which is going to be really efficacious like this, but with greater safety and perhaps greater versatility, because right now it was just working in, in ALL leukemias and in lymphomas. And so we came up with what's called the switchable CAR T-cell platform, and that's where we use an antibody to turn on and off the cells. And so now the cells are given to the patient, but the cells are inert, essentially they're off. They just sit there and they wait until we dose the patient with an antibody that turns the cells on and allows them to recognize the tumor. The advantage there is that the cells get carried away. We simply don't give any more of the antibody and the cells will naturally turn themselves off in the absence of the bodies. So it is, it's a way of thinking about it, like a, a safety switch.

Drew (14:28):

Wow. That's amazing. So yeah, antibodies and T cells communicate with each other. And so by giving the antibody, and I assume the amount of antibody, you can almost use it like a dial to sort of boost up the T-cell response or sort of dampen it down, if you don't give any?

Travis (14:43):

Yeah, I I've called it a switch, but then people ask me how it works. You know, functionally as a switch, it's more like a light dimer. Mm. Uh, if you, if you're able to tune, like you said, or titrate the response to a, to a therapeutic index, which you, you hope is gonna be safe and efficacious for patient,

Drew (15:00):

That's such a cool idea. So how fast acting is this treatment?

Travis (15:06):

It's very fast. So the cells, when they're infused back into the patient, a typical CAR T-cell will activate and expand within between a couple of days, maybe one to three days and maybe seven days to two weeks. That's, that's kind of the timeframe where you'll see the peak expansion of those cells in the patient. But it's, it's so incredibly fast that when they were first running these CAR T-cell trials, typically a patient comes in, they get a scan, right? They get a baseline assessment of their tumor burden. Then they get CAR T-cells and then the next time they get an assessment of their tumor burden via a pet scan or CT, or, um, uh, MRI or whatever it is that's appropriate for their disease. It's usually at 28 days, it's

usually about four weeks later. And, uh, some of the anecdotal reports from physicians that were involved in these early stage clinical trials for CAR T-cells was that they were holding the scans up next to each other. And they said, is this the same patient? Because they could not find any residual disease in the patient just four weeks later. And they had not seen anything like that with chemotherapies or with any other type of treatment paradigm, except for surgery where you're resecting the tumor. Right. So it's incredibly fast compared to what cancer, uh, researchers and oncologists had been using historically. But that speed is what makes it so dangerous is because it's such a vigorous response of the immune system.

Drew (16:37):

All right. That's why it needs the fine tuning. That is incredible. I mean, do you, when you think about this stuff, do you think of this as a cure for cancer?

Travis (16:47):

Yeah. We talk about cure and curative responses, but I think when we talk about cure, it's all about how long, how long does the patient remain in remission? That's, uh, a difficult question to answer because the field is so young still, and there was a very high profile, uh, article coincidentally also published by the folks at UPenn on now the 10 year follow up the cancer patient that he had done in their early 2000 tens. And they still are in remission. Some of those patients, and you can still detect the CAR T-cells. Are those patients cured? Are they cured? Um, possibly, um, 10 years is a really a, a, a long period of time to go without any residual tumor. But I think it's gonna take time to know whether it truly is a cure where that cancer will, will never come back again. But so far it looks quite promising.

Drew (17:43):

Sure. Yeah. Good point. I mean, you need this response to be so durable that we might be kind of older gentlemen, by the time it might be recognized as a cure…

Travis (17:53):

Right. Right.

Drew (17:56):

And so, as far as I know, the team at Calibr have recently had some success, uh, in some clinical trials, am I right in some preliminary results with this type of switchable CAR T-cell platform?

Travis (18:08):

Right. So we announced the first preliminary data for our CAR T-cell our switchable CAR T-cell, uh, studying patients with B-cell malignancies, which would be lymphomas and leukemias. We announced that at the American Society of Hematology conference in December. I'll give you a little background on the way that the study works in patients, which is very similar to any type of a clinical trial, which is that we gotta start at the lowest doses. Um, and we've got two components, we've got our CAR T-cells and then we have our antibody-based switch. And so we started with the first cohort at the very lowest dose, um, of both because we wanted to make sure first and foremost that we, it, it was going to be safe, uh, to administer it to patients. Um, and so, you know, we were really pleasantly, I don't wanna say surprised because that would suggest that we didn't think this was going to work at the lowest doses, but we were, uh, very impressed including myself at how well it worked at the lowest dose. So two of the first three patients at the lowest doses experienced complete responses of their tumors. And so it

was really remarkable and really gratifying to see we started this project almost 10 years ago. So after 10 years of working on something to finally get it into patients and to see such a robust response in just the first couple of patients, it was a great moment for, for the entire team that had worked on this.

Drew (19:31):

Definitely. Yeah. Sounds quite emotional actually. And did you see any, uh, negative side effects?

Travis (19:37):

We did see, uh, what we call low grade cytokine release syndrome (CRS) and low grade, what we call, uh, what the field calls, ICANS, which is a type of neurotoxicity. Generally when they're low grade, it can be as mild as a fever, and it is indicative that these cells are active and they're working and so long as we can keep it at that low grade managed with just some, some Tylenol and rest. I think that's what we want to be able to do with the switch. The next step here is gonna be able to demonstrate that we can avoid the overactivation of the, uh, immune response, uh, and keep it from going to higher grade CRS, which is where you run into really big challenges with patients getting sick and, and dying. And we did show, we have early evidence in that, in that study as well, that when we stop dosing, the switch molecule.

Travis (20:32):

So the switch I should say is dosed on a cycle. So it's dosed, um, every day for a week followed by three weeks of no dosing. And then you come, the patient comes back into the hospital that they're dosed for another week with the switch. They don't get any more cells. The cells are only given once at the beginning. So they just keep getting this antibody-based switch. Uh, we did show that when, uh, the switch was stopped being dosed a patient with low grade CRS, didn't continue on to a higher grade of CRS, their CRS resolved within, uh, a couple of days. And so that was really good evidence for us that this functioning as a safety switch was working as intended.

Drew (21:12):

Wow. That is great news. So if we think about that person with say leukemia, which is one of the examples, would this therapy work at all levels of severity? So does the, the more severe, like advanced, uh, patient respond better to this or does it all just depend on the level of that switch?

Travis (21:33):

Yeah, so you're saying later stage tumors. Sure. Do later, later stage tumors respond as well? We don't know yet. We haven't rolled enough patients to, to know that you could think about this in, in a way in which the ability to tune or titrate the level of, of therapy would be very effective in, in hyper personalized medicine, where somebody comes in with a tumor and that's very large and perhaps you dose the appropriate amount or that tumor that's a possibility in the future. And it it's certainly enabled by the technology. We sometimes refer to the technology as a software and hardware based approach. Our CAR T-cells are the hardware and the switch is the software, and we're able to program our hardware to go where we want it to go and do what we want it to do and turn on when we want it to turn on using that antibody based switch. So thinking about it like that. Yes. Uh, it could be used in the future for patients with different grade tumors to come in and have their cells programmed appropriately.

Drew (22:35):

Got it. Yeah. I can almost envisage this almost like a menu. So you come in and, you know, you have this size and grade tumor, okay. You need this, you know, amount of cells, this level of antibody…

Travis (22:48):

Right. And that's, so that's the real potential of the platform that we see in the long run is that this right now we're demonstrating this in, in B cell, leukemias and lymphomas, which is where other CAR T-cell products have not only worked, but have been approved. There's approved products on the market for B cell malignancies for, for CAR T-cells. And so we know it's a very competitive landscape and we know patients will have other options in that space, but the ability for this to work, not only in B cell malignancies but also to then work in, in other diseases like solid tumors, where CAR T-cell have not worked for a variety of reasons, including toxicity as one of the number one reasons why it's difficult to get CAR T cells to work in solid tumors, using the switch as almost a menu of options to program for the solid tumors, we think is gonna be very, very important in seeing success for CAR T-cells and solid tumors.

Drew (23:45):

Got it. Yeah. I was gonna bring that up, because like you said, it's all been tried in different types of blood cancer and wow. Yeah. It would be such an amazing impact if this was available for say like lung cancer or breast cancer.

Travis (23:59):

Right. And that's where AbbVie, who's our partner on this program sees potential. They are very interested in taking this into solid tumors. So they're working with us on a suite or a menu of options of different switches, uh, for solid tumor indications so that, you know, once we're successful in our B cell malignancy trial, that will enable them greatly in their solid tumor trials because we'll have a really good understanding of how those cells behave in patients. And now they're just gonna take that hardware and they're gonna program it with a different software.

Drew (24:34):

Wow. Fascinating area. Looking even further ahead, I do have a crazy idea for you. Do you think this type of therapy would be feasible for people with different autoimmune diseases? Because I know, uh, we have other types of T-cell ones that help sort of dampen our immune system, like our regulatory T-cells. So do you think there's any way we could reengineer those?

Travis (24:56):

Yeah. That's a really interesting idea. And I have a collaboration with Dwight Kono at Scripps on using CAR T-cells for patients with lupus. So I think that the way that we built this platform, it's agnostic to cell type. Right now we're putting it into effector cells to, uh, effector T-cells to eliminate cancer cells. But like you said, you can also envision doing this in regulatory immune cell types or in other effector cell types for other types of cancers. Um, and you know, the potential there could be really, really broad.

Drew (25:30):

Wow. Yeah. This seems really, really promising for the future.

Travis (25:34):

Yeah. The, the field is at this incredible inflection point right now with immunotherapies, you know, it'll be really exciting over the next several years to see where it goes when chemotherapies first started being used, it was tried one at a time. And, and you know, it took a long time to figure out which chemos worked and which, and which cancers and then combos started to occur. And now if you hear about, uh, any patients, uh, early, or, or their first stage chemotherapies, they're all acronyms, right? Because they're all so many different chemos that are involved in a combination. It's gonna be the same for immunotherapies. We're using CAR T-cells right now and switchable CARs. But over the next 10 or 20 years, we're gonna see combinations of all of these different types of immunotherapies, which is gonna make them all the more effective. Hopefully it won't just be a selective number of patients who have that really durable response last 10 years that we're reading about in the news, but it's gonna be the majority of patients have that really durable response.

Drew (26:37):

It really is life-changing work. It just, I can't wait to see all the successes, which I'm sure are only sort of a few years away. Yeah. Cool. Well, when you're not in Calibr and uh, you know, working hard on these gene therapies, what are your other passions? You mentioned that you, you may or may not be wearing board shorts right now. So have you been, have you been surfing lately?

Travis (26:57):

Uh, yeah. So I get out in the water. I try to get out in the water a couple times a week. We've got two little ones at home. Now we've got a one year old and a three year old, uh, who keep us, keep us busy. And so hopefully I'll get them in the water in the next couple years and then they can join me, join me in the mornings.

Drew (27:13):

Oh, that would be so cool. Yeah. I was just at the conference, uh, up in the mountains and manage to get out and snowboard for a few days. And it was amazing. Seeing must have been like a couple of three year olds just being sort of taught to snowboard and definitely inspiring. I could see, see you with your little ones on those little surfboards. Yeah.

Travis (27:35):

It's so cool because they've got such a low center of gravity and it doesn't seem like, you know, when they fall, they don't have very far to go. That's why it's, it's easy. It's easy to learn at that age. I feel like when you, by the time you get to be an adult, the snow looks very, very hard. I feel it looks way harder than it does when you're a kid.

Drew (27:53):

Cool. Well, I'll just wrap up with my, uh, final roundup question that I like to throw all my guests, which is if you could give one piece of advice or your wisdom to anyone in the realm of work or career progression, life, health self-improvement, whatever it is, what do you think it would be and why?

Travis (28:09):

I gotta sound like some type of a sage here… I, uh, instead I'm gonna steal somebody's quote. When folks come into my office and were talking about projects, I, I tease 'em a lot. I say in God we trust, all

others must bring data, which was actually, I think there was a statistician named Edward Deming, who originally said that. It's not a religious statement at all, but what I explained to people, it's put all of your, your beliefs, your preconceived notions, your prejudices, everything else aside, when you're doing science, everything that's gonna cloud your thinking and just isolate it down to what is the data? What are you working on? And what is the long term goal of what we're doing? You know, keep the big picture in mind and everything else will, will kind of coalesce out of that. And we hit a roadblock and we can't figure out which way to go. It's really important to always kind of center us, bring us back to that, that notion that what does the data say? We're in a field where it's based on data. And so let's let the objectivity, you know, kind of rule.

Drew (29:08):

Sage wisdom indeed, there from Travis. And I must thank him and all the folks at Calibr and Scripps Research, working in this space, dedicating themselves to improving the lives of patients everywhere who may have very little options for treatment. Remember that you can show us your appreciation by giving us a review and a rating on your podcast app of choice, every little helps so that we can continue to bring you this content. We'll have more links to Travis's work in the show notes as well as links to our Scripps Research Magazine. So remember to check those out. And so until we meet again for more cutting edge science, stay curious and be well.