

Support for Yale Cancer Answers comes from AstraZeneca, a biopharmaceutical business with a deep-rooted heritage in oncology and a commitment to developing cancer medicines for patients. Learn more at astrazeneca-us.com Welcome to Yale Cancer Answers with doctors Anees Chagpar and Steven Gore. I am Bruce Barber. Yale Cancer Answers features the latest information on cancer care by welcoming oncologists and specialists who are on the forefront of the battle to fight cancer. This week, it is a conversation about cellular therapy research with Dr. Michael Hurwitz. Dr. Hurwitz is an Assistant Professor of Medicine and Medical Oncology at Yale School of Medicine and Dr. Gore is a Professor of Internal Medicine in Hematology at Yale and Director of Hematologic Malignancies at Smilow Cancer Hospital.

Gore As someone who has worked with and takes care of patients with prostate cancer and kidney cancer, what is all this about cell therapy?

Hurwitz Yes. One of my interests is using any immunotherapies to treat a lot of these diseases.

Gore What is immunotherapy?

Hurwitz We know that the immune system can attack cancers and can in fact get rid of a lot of cancers that we have in the body. I would say, in the last 10 years or so, there have been really major advances in figuring out how to activate the immune system in a situation where it is not working, to get it to work to kill off cancers. And the way that it has had a lot of success recently is we actually inject antibodies in the people and these antibodies are proteins that can actually turn off signals that cancers produce to turn off the immune system.

Gore So, there is a cancer cell and it sees a tumor cell, no that is the cancer cell and it sees an immune cell and somehow it has got like a force field, it says forget about it, you cannot hit me, something like that? I am thinking Star Wars.

Hurwitz A little bit, but basically the key point is that the immune system is a set of cells in the body that recognizes things that are foreign.

Gore Right, and they are roving around. Just like one of those lunar rover things?

Hurwitz That is right. They are roving around all the time. Gore Got their laser guns ready to go...I am going to Star Wars here again. Hurwitz You are going to Star Wars. Actually, they probably have their lasers on safety, not always going in fact.

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Gore Okay, that is good to know.

Hurwitz However, when they recognize something as foreign, it is different, they will attack it and try to destroy it and that is what it is supposed to do.

Gore Right.

Hurwitz Now, if you imagine every time you get a cut, something like that happens, bacteria gets into the cut, lots of cells from the immune system go into where that cut is, they cause swelling, they cause more cells to go in, they get rid of the bacteria but you do not want that to go on forever because if that went on forever, every time we got a cut, we would lose our finger or it would blow up like a balloon. Gore Inconvenient.

Hurwitz Very inconvenient. So, the immune system also has off switches built in and has cells that actually turn things off.

Gore So, that is like the commander coming around saying mission done, let us go home. Hurwitz That's right, and in fact, the things that are injured even have, they can turn off the off switch. Gore Leave me alone I am already there.

Hurwitz And PDL-1 is probably the most famous off switch, and what PDL-1 does is it is the off switch that hits something called PD-1 which is on immune cells, and you have seen ads for these drugs that block it. And that hits the off switch, which is PD-1 on the immune cells.

Gore I would say call them off and on switch that would be so much easier.

Hurwitz Unfortunately, many cancer cells have figured this out to speak anthropomorphically since they do not figure anything out, what happens is, many cancer cells...Gore They evolve that way? Hurwitz They evolve that way and make PDL-1 and turn the immune system off.

Gore Wait a minute. So, they make their own off switch?

Hurwitz They make their own off switch, exactly.

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Gore Sneaky.

Hurwitz Quite sneaky. And of course, it is more complex than that. There are other on and off switches, but that is the basic idea. And the antibody drugs are actually quite good at fixing that problem.

Gore Turning the off switch on again?

Hurwitz Turning the off switch on again or at least making sure that the cancer cannot hit the off switch.

Gore Okay, that is cool.

Hurwitz And the result of that is that for a disease like melanoma, which is a disease that if it had spread already, which we call metastatic, it kills about 95%

of people within 5 years. Now, that rate is improved to about 50% of people. Gore Not good enough, but a lot better.

Hurwitz Right, not that great but much, much, much better. In other diseases, it is not as dramatic, but there have been long term people doing very well with lung cancer, with kidney cancer that has spread, with bladder cancers, a whole list of these cancers have been improved with this, but obviously we are not there yet. The best one is melanoma, which is like 50%. So, there is a huge amount of work being done on other things like this, other on and off switches, but another approach is to weaponize the immune system differently and one of the ways that we have been doing it is by something called cell therapy.

Gore So you are talking about re-arming the Jedi fighter thing with some other kind of mechanism or bringing in a different fighter? Yoda?

Hurwitz Actually no, trying to think of analogy, I think Yoda was there, but...

Gore I realize it is getting lame, but I am dug in this deep already.

Hurwitz Yeah, unfortunately I am only good with the first 3 movies.

Gore You mean 4, 5, 6.

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Hurwitz Actually, the cell therapy is a relatively broad term, just meaning that we are going to use immune cells to attack the cancer directly. So, rather than putting in an antibody, which is a protein which can as we said block the on-off switch, we are going to actually try to take the immune cells themselves, do something to them to make them even more active, put them back in a person.

Gore Even though the cancer may still be saying, I have got the off switch, I have got the off switch?

Hurwitz Yes.

Gore Some day, you are going to overcome that somehow?

Hurwitz We are going to try to overcome it.

Gore Okay, I got that.

Hurwitz So, something we are actually not doing, but I know that you are doing, is something called CAR-T cells.

Gore Don't give me away.

Hurwitz Yes. So, you could talk about it as much as I could.

Gore I would rather have you talk about it, you probably understand it better than I.

Hurwitz Again this has been in the press and people may have heard of this many times, in a CAR-T cell, what you are doing is, I kept talking about immune

cells, immune cells, there are a lots of different cells in the immune system, but one subset are called T-cells.

Gore T-cells are those cells that people may have heard about during the HIV/AIDS day. So, those T-cells are the ones that went away from the HIV virus and caused infections, right? Those are the same kind of cells?

Hurwitz Exactly. And there are sort of 2 flavors. One flavor is called the helper T-cell and one is the killer T. So, the helper T are the ones that went away I think in HIV. Gore I want some of those.

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Hurwitz So the killer Ts are the ones that actually find the things that they want to kill and destroy, and they are insanely effective at it.

Gore Luke Skywalker, come on.

Hurwitz Yeah, they are awesome. And in CAR-T therapy, CAR stands for something called chimeric antigen receptor.

Gore Nothing to do with the vehicles?

Hurwitz Nothing to do with the cars, absolutely no, that's right.

Gore You know that red car in the movie?

Hurwitz Exactly, not that. So, with CAR-T cells what we are doing actually is we are taking out T-cells that we know desperately want to kill all the time. However, what we are doing is we are deciding what it is going to kill and we are doing it by taking a piece of DNA, putting that piece of DNA into the cells, we are taking T-cells out of a person.

Gore A person who has cancer?

Hurwitz A person who has cancer. And then, we are adding DNA into these T-cells and that DNA encodes something and what it encodes is something that targets T-cells for the cancer directly.

Gore Like a killer instinct?

Hurwitz Like a killer instinct. And it works phenomenally well for certain diseases.

Gore So now these cells are outside the body, how is that helping?

Hurwitz That's right. So, you can re-inject them after giving someone chemotherapy to remove what is there already. You want to actually remove a big chunk of the immune system that is there already.

Gore Just to make some room right?

Hurwitz For a few reasons. One is to make some room. Two, remember I said that the immune system is not just killers and things that activate killing, there are also part of the immune system that turn things off.

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Gore There we go again, the on and off switches.

Hurwitz We call those T-regulatory cells. You want to get rid of those. And the last thing that you want to do is, these cells produce signals throughout the body all of the time and some of those signals are inhibitory signals of the immune system and we want to get rid of those too. So, all this stuff by the way was figured out in mice that there are great mouse models showing that if you do not do all those things, you really do not get a great job by putting T-cells back in. As you pointed out, they need room to grow and they need to do it when they are not being blocked.

Gore Just don't bother me.

Hurwitz Let me do my job, give me space to live, etc. So, that is what they do. They take these T-cells out, they put something into the T-cells to target them directly to what they want to kill. Then, they give the patient eventually chemotherapy to remove plenty of the immune system that is there and they put these back in, and as you know actually better than I, they have had great responses in acute lymphocytic leukemia.

Gore Childhood leukemia that has been resistant to treatment.

Hurwitz Exactly. So, that is great. Unfortunately, that has got some problems for treating what we call solid tumors, which are about 90% or 85% of adult cancers, which are things like what I treat – prostate or bladder, kidney, melanoma or lung.

Gore Well, what is the problem? Why can't you just give them like killer instincts about the prostate?

Hurwitz Right, so there are some real differences biologically in the solid tumors and what I was calling sort of liquid tumors, the tumors that come from the blood system, and one of them is that there really are not that many great targets that are consistent across the board.

Gore From tumor to tumor?

Hurwitz From tumor to tumor, which is what you really need for the CAR-T because otherwise it is very inconvenient. And even more, even within a single tumor, it is rare that the antigen, which is the name of the target, it is rather the target that is really required and one of the things about cancers is that they evolve as they grow. And so, you might be able to target some of it with a specific target but then that target will be lost.

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Gore So, the cancer says ha-ha, I am just not going to show you that thing anymore and you can try to target me all you want, but you can't take away the target.

Hurwitz Exactly. So, it turns out that the approach of not using CAR-T's is different in sort of a big way. Gore You are about to tell me something about a different approach?

Hurwitz A different approach. Gore Okay.

Hurwitz And the approach has to do with this. This is again pretty important. If you look in tumors, a lot of the time they will have these killer T-cells stuck in them, around them, and if you actually analyze those T-cells, it turns out they are recognizing the tumor.

Gore So, why isn't the tumor dying?

Hurwitz There are a few reasons, but one of the big ones has to do with this whole off switch.

Gore They are there but they have been turned off?

Hurwitz They are there but they have been turned off.

Gore But they do not die, they just sit there.

Hurwitz That's right. But they are not dead.

Gore Twiddling their thumbs if cells had thumbs.

Hurwitz Exactly. And there are other reasons, but that is probably the major reason. There are multiple different off switches, they have been turned off. And so, however, they are probably not just recognizing one target. Each of those T-cells might be recognizing a different target. So, if we could take all those T-cells out, grow them up outside the body and put them back in, now you have got T-cells and if you could make them active again, they are active against multiple targets.

Gore Wow! This is getting complicated. So, complicated that I am going to have to take a short break for a medical minute and catch my breath. Please stay tuned to learn more about cellular therapy research and clinical trials with Dr. Michael Hurwitz.

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Gore Welcome back to Yale Cancer Answers. This is Dr. Steven Gore. I am joined tonight by my guest, Dr. Michael Hurwitz, and we have been discussing immune and cellular therapy research, and Mike before the break, if I got this right, you were telling me that in these kidney tumors that you study and other kinds of tumors that arise in organs, you could see these wannabe killer cells kind of sitting there all ready to go, but they have been turned off so they are just kind of sitting there helpless, but each one might be really looking at a different protein on the cancer cells, right? So, they would not be subject to the problem that you talked about before where the cancer cell can say ha ha ha, I am taking away my target right?

Hurwitz Yes. I mean, it is all the matter of degree and theoretically the cancer could lose every one of these targets.

Gore Okay, let us continue that. Did you say you are going to take these cells out, how are you going to do it? Are you going to go in there and suck them out?

Hurwitz That's right, and we are actually doing this now with the patient and believe it or not, the technology to do this, the basic idea is from the early 1980s. The idea is not terribly new but now we are doing more variations on it and we probably know much more, but what we really do is you have a patient who has a cancer that has spread and you take one of the spread cancers out of the person's body.

Gore A tumor?

Hurwitz You take a tumor out, and we grind it up in a very controlled way.

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Gore Sweeney Todd or anything like that?

Hurwitz This is nothing like Sweeney Todd. There is no meat grinder, none of that just the actual tumor.

Gore No meat pies?

Hurwitz No meat pies, absolutely not. It is done in a very special facility that has to keep everything incredibly clean because some of the stuff that we take out is going to go back into the patient. So, the cell therapy lab at Yale takes this tumor out, they grind it up as I said, and you grow it in a dish, particularly

the growth medium is good for immune cells but not for other cells. And what happens is the tumor cells die off and the immune cells grow. And the nice thing about it is that as these immune cells grow, they lose those off switches.

Gore Really?

Hurwitz Yeah. They will lose off switches if you grow them in an activating environment and we do. We take the things that the immune system uses to activate itself and we throw that stuff into the mix, they grow up very active. And then, we do what I talked about before with CAR-T cells, then we treat patients with chemotherapy.

Gore To make the space and all that, get rid of some of those.

Hurwitz Get rid of the suppressive stuff and then put it back in. And as you might imagine, it is a bit of a dance. The timing has to be right. You have to take the tumor out, then our cell therapy lab is continually seeing exactly how things are growing to make sure that A -- nothing bad is growing in there like bacteria and B -- that they are growing at the right rate. And then when you know that there are going to be enough cells, only then do you give people chemotherapy. It is not exactly cool to give someone tons of chemotherapy and knock out their immune system if you do not have something to put back in. So, we try to do no harm, as you know. So, that is done and then we have to admit the patient to the hospital and then we give them their cells back. And once we give them their cells back, then we give it a boost. We then give the patient even more of something called interleukin 2, which is something produced by the immune system to activate itself.

Gore Kind of like a hormone?

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Hurwitz Kind of like a hormone, exactly.

Gore But why doesn't the tumor cell turn it off again, turn the new cells off?

Hurwitz Right, the hope is that you have given enough.

Gore Enough cells you mean?

Hurwitz Enough cells that it just sort of overwhelms them. The studies that were done, these were done maybe 10 years ago, had what is called a response rate of about 30-40%. So, in other words, in people in whom we did this, about 30-40% of them, their tumors would shrink. A much smaller group of them, would have them shrink for very long periods of time. And that is great. These days, we are not as good at it. Why? The technology is just as good but it is just that the patients have already been treated with the antibodies for the off switches, and so the tumors are more resistant. So, now, the question is how can we improve the technology? So, the first thing that we are doing which is sort of obvious is as soon as we give back the cells, we are now giving them the

antibody drugs that we were talking about. So, that we are going to block the off switch at the same time that we are giving the cells. That is obvious, and we are doing that.

Gore Was not obvious to me.

Hurwitz So we are doing that and we are doing it pretty intensively. We are doing it with multiple drugs at the same time, which is unique. That is something that is only being done at Yale. And then, the next step that we are going to do is we are going to try to isolate, I said that there are T-cells that are within the tumor and those recognize the tumor, but some of them are more active than others and it turns out we know a little bit about what makes the ones more active and so we are going to do a technique to isolate those specifically.

Gore The super-duper ones?

Hurwitz The super-duper ones, and we know that in addition to that, in very, very tiny numbers, these T-cells probably leave the cancer and circulate in the blood. So, we are also going to look to see if we can isolate it from blood which would make it a lot easier on patients. So, there are a number of different routes that we are going to try to make it a better therapy and at the same time make it more tolerable for patients. And these are sort of the first things that we are doing. It is a pretty new program.

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Gore What kinds of cancers are you treating this way?

Hurwitz We are beginning with melanoma, which is the one that has been done the most and we are actively trying to get it done in kidney cancer and in lung cancer. And in order to do that, we need to first do a little bit more ground work, which is to actually take tumors out of people and analyze them and show the Food and Drug Administration that we can do all this safely. So, this is all pretty experimental, in that there is nothing standard about this, there are about 5 places in the country probably that are doing this.

Gore Wow. But there must be some companies that are trying to do similar things, do you work with any of them?

Hurwitz Yes. The thing I was talking about isolating the super-duper ones, we are doing that with a company. And there is another company out there that the whole company, all it does is these cell therapies, and they have done lung, they have done kidney cancer; however, if we are going to make the cell product ourselves, the Food and Drug Administration considers it a separate new drug, and that makes sense -- you want every place that is doing it to do it right. And furthermore, we want to do this ourselves because we want to improve the cell growth technique. That is another area of the research that is really important. And furthermore, one of the things that is interesting from a scientific standpoint is when you are taking tumors out of people, and you

isolate the immune cells, we got all that tumor there, you can also analyze the tumor and maybe we can figure out who is going to do better with this therapy and who will do worse with the therapies so we do not put them through it and whether we can manipulate the cells in certain ways depending on what the tumor shows. So, there is a lot of investigation to be done, it is all very new.

Gore As you described it so far, I go through surgery to take out a metastatic tumor, hopefully it is somewhere superficial, close to the surface, let us just take the best-case scenario, and you grind it up and everything is fine, you gave me some chemo and I know that your chemo is not so terrible compared to some chemo, so not so bad and now are you giving me this injection, what is the big deal, it seems like pretty easy peasy right, so then the patient just goes home and everything is fine?

Hurwitz There are a few reasons. One is that, so far we have not done it to people who have early disease, we are giving this to people who have been pre-treated already with the more standard therapy. So, these are people with later disease, often growing rapidly, and they can get sick pretty rapidly. Secondly, there is a built-in wait time

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because once you take the tumor out, remember I said you have to let cells grow out and that is a few weeks, we have not gotten less than 3 weeks, and we are working on that, but we have not gotten it less than 3 weeks. And then, in patients like this, the chemotherapy can hit them pretty hard and remember I said that once we give them their cells back, we give them this thing, like you said like a hormone, this IL-2 thing, now IL-2 is one of the mediators of the immune system that activates the immune system. So, the audience probably is not aware that a lot of the times, most of the time when you have the flu, the reason you feel so horrible with the flu is largely because of the immune system's response to the virus and not the virus itself. And that is the same with IL-2, interleukin-2.

Gore You are giving people the flu?

Hurwitz We are giving people the worst flu they had ever had. So, your blood pressure drops often, lot of nausea, incredible fatigue, you become very swollen because there is something called capillary leak syndrome which means a lot of the blood can actually seep out of the tissues. It is not a picnic by any means.

Gore That does not sound like fun at all.

Hurwitz It is not. It is not as bad actually now, we used to do it for patients just that alone for people with melanoma and kidney cancer because that alone in those cancers sometimes was enough to activate the immune system that was there. These patients do a little better than those patients because unlike those patients who had an intact immune system, we have already removed most of the immune system, so they do not get as sick usually, but still they can and

it is a tough therapy for people who are already quite ill sometimes from their cancers.

Gore I see. It really sounds very complicated. And how soon before you know whether the cells are working or not or whether they are effectively shrinking the tumor?

Hurwitz We check about 6-8 weeks after and you will see responses sometimes then.

Gore It is a one-shot deal, you get your injection and that is it, once it is done?

Hurwitz So far it has been that way, but we are already planning on not making it a one and done. We are planning on having repeated infusions depending on the particular question that we are trying to ask. And it has to do I think a lot with this idea that we already spoke about, which is that tumors change overtime, and so, you can imagine that you would want to adjust the cells to respond to the changing tumor.

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Gore So, would you take out another tumor and start all over again?

Hurwitz The other thing that can happen, one of the other ways that tumors become resistant, which is sort of amazing and a number of groups have figured this out, one group at Yale and some groups at Sloan Kettering and some other places is that the way that our immune system recognizes, most of our immune system recognizes things that are foreign is that when our cells have something abnormal in them like a bacteria that invaded or a virus, they actually have baskets that are on their surface of the cells and the baskets contain that foreign stuff.

Gore Kind of waving it around?

Hurwitz Waving it around, saying hey there is something going on here and we call that MHC. That is the name of the basket. Which stands for major histocompatibility complex.

Gore But SOS basket would have been better.

Hurwitz SOS basket would have been a delightful name.

Gore And for some other Star Wars analogy.

Hurwitz That is right, that's right.

Gore That is a hologram to princess Leia.

Hurwitz It turns out that cancer cells have figured out in certain cases -- when you treat them with some of these antibodies that block the off switch, they have learned to stop making MHC altogether.

Gore No more SOS baskets?

Hurwitz No more SOS baskets, and at that point, most of the immune system does not recognize them at all.

Gore It has got the shield of invisibility.

Hurwitz That's right.

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Gore Harry Potter wise.

Hurwitz Harry Potter I am actually pretty good on.

Gore Okay, if you would have told me, I could have done them. I am converse in Harry Potter.

Hurwitz However, fortunately, there is a subset of cells in the immune system specifically designed to recognize things wearing invisibility cloaks, and they are called NK or natural killer cells, and some day maybe we will do some sort of tandem thing with first regular immune cells and then NK cells, I mean there are many directions that we could go with this. It is a matter of us getting grants as such to do those things and moving forward.

Dr. Michael Hurwitz is an Assistant Professor of Medicine and Medical Oncology at Yale School of Medicine. If you have questions, the address is cancer-answers@yale.edu and past editions of the program are available in audio and written form at YaleCancerCenter.org. I am Bruce Barber reminding you to tune in each week to learn more about the fight against cancer here on Connecticut Public Radio.