



CAR T-Cell Therapy

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(Hematology)

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Welcome to Yale Cancer Answers with doctors Anees Chagpar and Steven Gore. 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 CAR-T cell therapy with Dr. Iris Isufi. Dr. Isufi is an Assistant Professor of Medicine and Hematology at the Yale School of Medicine, and Dr. Gore is a Professor of Internal Medicine at Yale and Director of Hematologic Malignancies at Smilow Cancer Hospital.

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Gore CAR-T that sounds like something we have never heard about, what the heck is CAR-T?

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Isufi That is what I said a few years ago when child was treated for this therapy who had aggressive leukemia and achieved remission. Since then, a lot has happened, many patients have been treated, we have 2 new drug approvals and are treating patients throughout the United States

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Gore Okay. Can you tell us sort of generally in a lay term what this is all about?

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Isufi Yes. So, we are taking T-cells which are immune cells from individuals with cancer, genetically modifying them in the lab, expanding them to produce more and putting them back in the patient after they receive treatment.

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Gore No, wait a minute. So, T-cells, are not those the cells that are like missing in HIV patients and stuff?

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Isufi That's correct.

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Gore So, these are cells that fight infections?

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Isufi Those are cells that typically fight infections, particularly viral infections. They interact with many other cells in the body and are actually very important to also fight tumors as well.

02:12.700 --> 0:02:13.1

Gore The cancer cells?

0:02:13.1 --> 02:14.200

Isufi The cancer cells.

02:14.200 --> 02:25.400

Gore Okay. So, I am with you so far. So, now we have got a patient who has got cancer and you are taking some of these T-cells out, how do you get them?

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Isufi So, we get them through a process called apheresis. The patient sits in a chair, they are connected to a machine and they sit in the chair for several hours. Their blood is filtered through that machine...

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Gore So, the blood goes out of one arm...

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Isufi And back into the other arm.

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Gore Gotcha, but through the machine in the meantime?

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Isufi Through the machine in the meantime, which sorts out their T-cells because they have markers on their surface and they are recognized as being such. The blood is put back into the patient and we send the cells to a company outside of our institutions usually where they get genetically modified.

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Gore Hold on. That sounds scary. Is that like what they did in China where they would, I guess they were doing designer embryos and stuff like that, nothing like that right?

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Isufi This is a very carefully controlled process. It is very carefully monitored by the Food and Drug Administration and it is a very rigorous process. It does not involve any stem cells. This involves T-cells that are circulating in the patient's blood stream that are normally there. We are only genetically modifying these cells to recognize something on the tumor cell for targeting.

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Gore Can you explain that to me a little more so exactly what are you putting in the DNA of these cells, like what kind of thing?

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Isufi So, what we are putting in in the cells is actually a receptor that the T-cells have inside them. What we are doing is we are just changing small parts of that receptor to recognize a target on the cancer cell, the tumor cell, and we also change other parts of that T-cell receptor that will eventually make the T-cell make many more copies of itself to target as many tumor cells as possible once put back into the patient.

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Gore Okay, so you are making it kind of like super-attack cell?

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Isufi A super-attack cell and a cell that is going to eventually be able to make hundreds of thousands if not millions of copies of itself once it goes back into the patient's body.

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Gore It reminds me of that Star Wars movie where there were making clones on that planet, kind of scary?

05:02.400 --> 05:22.400

Isufi It is actually not a scary procedure for the patient to get the cells out. We give chemotherapy before the cells are put back in, so that we quiet down the patient's immune system so that they are able to tolerate these cells very well once they go back into them.

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Gore I see. So, how long does it take to manufacture these new cells?

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Isufi It typically takes about 3 weeks to manufacture the cells and we are definitely making strides in shortening that process so that we can deliver this type of therapy to patients as soon as we can.

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Gore Okay. So, let us say I am a patient who is a candidate for this thing and I have gone to this machine and you took out these T-cells and you sent it out to wherever you are sending it out and I guess you do something to keep me quiet in the meantime or healthy in the meantime, right; and then what happens 3 weeks later when you get the cells back?

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Isufi So, when we get the cells back, we are able to admit the patient to the hospital and give them the chemotherapy part of the treatment, and then we infuse the T-cells. We are starting to gain more and more experience with this treatment, so the hope is that in the future, most of this therapy will be able to be administered in the outpatient setting.

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Gore Why do they have to be in the hospital at all?

06:32.700 --> 06:49.200

Isufi They have to be in the hospital initially for us to monitor some potential side effects that can happen after this type of therapy is delivered. There are 2 in particular that we worry about the most. One of them is called cytokine release syndrome.

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Gore That is a mouthful.

06:49.700 --> 07:54.900

Isufi It is a mouthful for sure, and the other one is called neurologic toxicity. And basically what is happening that once we deliver these T-cells into the patient, they make many copies of themselves, they target the tumor cells all at one and certain proteins can be released in the bloodstream that cause the patients to have very high fevers, they can feel like they have the flu even though they do not. We screen them for infections, but this is just a known side effect now of this particular therapy. They can get sick, but we have identified good measure to support them including new therapies that were not initially approved for these indications such as treating cytokine release syndrome. We have antibodies now that are on the market that are approved to treat it and we also oftentimes treat it with steroids.

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Gore So, I mean this does not sound so bad to have the flu. I mean, we have all had the flu like I do not usually go to the hospital when I have the flu, like what is the big deal?

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Isufi There are some patients that get sicker where they have difficulty breathing, they occasionally end up temporarily on a breathing machine or they can suffer problems with their organs. Usually, these are temporary and reversible for the majority of patients.

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Gore But really a big deal?

08:24.700 --> 09:48.700

Isufi But really a big deal. And that is why we are very cautious and especially in the beginning of this therapy, extreme precautions were taken to make sure that it was delivered as safely as possible for the patients and that all of the resources were there should they be needed. As you can imagine, if patients are having difficulty breathing or problems with their organs, the ideal place to be in is in a hospital setting where multiple subspecialists could be called to arrive to the scene as quickly as possible to help in their management. And the other toxicity we worry about is neurologic toxicity which usually starts with headaches and mild confusion and that is really the scariest aspect of it for patients and also for family members seeing their loved one who is having difficulty recognizing them or having difficulty writing and speaking. And this side effect is also treated with steroids and typically resolves back to baseline after 1 or 2 weeks.

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Gore So, it is not like a stroke or anything like that?

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Isufi This is not. We are not able to identify any abnormalities interestingly for the majority of the patients when we obtain brain imaging, such as CAT scans or MRIs and it seems that all of these side effects are transient and that they resolve back to baseline.

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Gore Do they understand or does anybody understand sort of what causes this neurologic toxicity?

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Isufi That is not yet fully understood. There are some hypothesis and some studies that are ongoing. We definitely know that these cells get into the central nervous system - the brain and the spinal cord. We do not think that they are directly causing damage, there may be things that are released that are causing damage in the brain and spinal cord. There are these cells called cytokines and there are other cells of the immune system called macrophages that go to the area, go to the rescue and sometimes those cause unintended damage while the T-cells are trying to fight the cancer cells. But we do know that the T-cells themselves get everywhere in the body and they are able to attack the cancer cells wherever they might be.

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Gore Wow! And you said that this neurologic problem is usually reversible?

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Isufi The neurologic problem is usually reversible.

11:20.900 --> 11:43.300

Gore Okay. So, you know, a few minutes ago, you had me in my chair, get my cells taken out, I was watching the movie or reading a book and just kind of waiting for my cells to come and I was thinking I was going to like you know open up my diet coke and get my cells, but now you got me in the ICU for 3 weeks. I mean, I do not know if I want to do this thing like. Why would I put myself through all that?

11:43.300 --> 13:02.400

Isufi So, we certainly screen the patients very carefully to see who qualifies and really needs this type of therapy. As you know, we have multiple treatments available for cancer patients that include chemotherapy, antibodies, targeted therapies. These are patients that have failed several different or where the disease has failed them, I should say. That the disease has really not responded to several lines of treatment or patients where we are considering doing a stem cell transplant, and one positive aspect of this type of therapy is that while there are toxicities, they are transient, they occur mostly early on in the treatment, in the first couple of months. There are no severe, significant long-term side effects as there can potentially be with transplant and the hope is that some of these patients who undergo this therapy will be cured and will never need treatment in the future, including sparing them a transplant.

[13:02.400 --> 13:10.000](#)

Gore Wow! That's very exciting. So, how effective is this therapy?

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Isufi The therapy so far has been approved for B-cell acute lymphoblastic leukemia.

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Gore That is another mouthful.

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Isufi Another mouthful, which is typically ALL that we see in children.

13:22.800 --> 13:23.900

Gore The good kind of cancer.

13:23.900 --> 13:39.600

Isufi The good kind of cancer for kids, but we that we also see in adults. So far, it is only approved in patients up to the age of 25 with leukemia and it is also approved in adult patients with certain kinds of non-Hodgkin lymphomas.

13:39.600 --> 14:04.700

Gore Alright. Well, that is a fascinating information, Iris, and I am certainly going to want to follow up and learn more about what happens to these patients with lymphoblastic leukemia and non-Hodgkin's lymphoma, but right now, we need to take a short break for a medical minute. Please stay tuned to learn more about CAR-T cell therapy with Dr. Iris Isufi.

14:04.700 --> 14:21.400

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This is a medical minute about lung cancer. More than 85% of lung cancer diagnoses are related to smoking and quitting even after decades of use can significantly reduce your risk of developing lung cancer. For lung cancer patients, clinical trials are currently underway to test innovative new treatments. Advances are being made by utilizing targeted therapies and immunotherapies, the BATTLE-2 trial aims to learn if a drug or combination of drugs based on personal biomarkers can help to control non-small cell lung cancer. More information is available at YaleCancerCenter.org. You are listening to Connecticut Public Radio.

15:06.600 --> 15:36.500

Gore Welcome back to Yale Cancer Answers. This is Dr. Steven Gore. I am joined tonight by my guest Dr. Iris Isufi to discuss CAR-T cell cancer therapy. So, Iris, let us get back to that pediatric cancer, the ALL, you know which we always hear as such a great success of the war on cancer and so many kids are cured without needing transplants and things, but I guess not everybody is really cured right? Some people are not cured, is that true? Some of these kids...

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Isufi Some of the kids are actually cured with CAR-T cell therapy.

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Gore No, I mean before with the standard therapy, not everybody is cured.

15:42.100 --> 16:04.500

Isufi With the standard therapy, not everyone is cured and certainly that is a minority of patients, but what we do now is that, with CAR-T cell therapy, they might not necessarily need to go to a stem cell transplant.

16:04.500 --> 16:06.500

Gore So, these are kids who did not get cured by their first chemo right?

[16:06.500 --> 16:24.200](#)

Isufi Correct. They did not get cured by their first and second chemotherapy and some of the patients may have already undergone transplants in the past.

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Gore And so, this CAR therapy or CAR-T therapy can put these patients back into remission and you say sometimes cure them?

16:30.000 --> 16:53.100

Isufi It can certainly put them into remission. It has very high response rate, this kind of treatment in childhood leukemia. We are talking 80-90% response rates, and about 2/3rd of those patients are actually able to stay in long-term remission without a transplant.

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Gore So, they just get this treatment once and they are done?

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Isufi Correct. And we can track these cells carefully and in the event that we can detect a small amount of disease in the patients' bone marrow or blood, we can still rescue them by doing a stem cell transplant.

17:12.900 --> 17:28.500

Gore That is really incredible. So, why is that restricted to just people up to the age of 25? Why cannot older adults with that disease be treated this way?

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Isufi Studies are undergoing to treat adults above the age of 25 and we hope that in the near future, we are going to get approval for that patient population as well.

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Gore I see. So, there is no reason to think that they should not be able to respond?

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Isufi There is no reason to think that they should not be able to respond.

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Gore Okay good. Just have not finished the studies yet.

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Isufi Correct.

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Gore So, what about these lymphomas that can be treated? How effective is that for those diseases?

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Isufi It is very effective for lymphomas as well. Remember these are also patients who have failed several lines of chemotherapy or have been failed by chemotherapy and for those patients, the response rates are not as high as leukemia, but fairly high compared to any other treatment we would offer. We are talking 40--50% cure rates even for that group of patients which is really remarkable.

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Gore And some of those patients might have had to have a stem cell transplant otherwise as well right?

18:25.000 --> 18:30.600

Isufi And many of those patients already had stem cell transplants using their own stem cells.

18:30.600 --> 18:35.100

Gore And the disease came back anyway?

[18:35.100 --> 18:35.400](#)

Isufi And the disease came back anyway.

18:35.400 --> 18:52.700

Gore So, that is really incredible. But I guess with these non-Hodgkin's lymphomas and these acute lymphoblastic leukemias, compared to all the cancers that still not a lot of patients right, I mean there is a very limited audience for this kind of therapy would seem?

18:52.700 --> 19:49.000

Isufi It is true. It is important to ask because I am a hematologist and that is what I treat, but obviously, non-Hodgkin lymphoma for example is the seventh most common type of cancer in the United States. So, ideally, the hope is that we are going to be able to expand the indication for CAR-T cell therapy to other diseases. So, there are multiple ongoing trials looking not only at other types of lymphomas and leukemias but also going into solid tumors, into cancers of the organs. And that is really very exciting and it has been challenging so far, but I have good reason and hope to believe that in the near future we are going to see that therapy expanded to solid cancers as well.

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Gore That is amazing. So, as I remember the first two commercial drugs to be approved or cells to be approved, it was just about a year and a half ago right that they were approved?

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Isufi Correct, in the summer of 2018, but things are moving very fast. The studies are ongoing throughout the world including Europe and Asia. And we are able to generate data at a very fast pace, really unprecedented before, everyone understood the importance of this type of therapy, everyone has been very willing to share their data and to share the management of the toxicities. So, even institutions who are not initially involved in the trials that lead to the first two drug approvals are now able to deliver this kind of therapy to their patients.

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Gore As I recall, Yale was not involved in any of the research trials initially, isn't that right?

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Isufi Yes, that is absolutely correct, and we were able to learn quite a bit from the experience of other institutions who led these trials and with hard work and a multidisciplinary approach within our institution for several months, really almost a year of preparatory work, we were able to offer this therapy at Yale.

21:20.100--> 21:31.600

Gore So, you mean, you could not just once they approved the drug, you could not just start doing it? I mean, we do a lot of complicated treatments here at Yale, why could not we just like start, give it once we can get it, I am surprised.

21:31.600 --> 22:35.600

Isufi Yes. And other institutions learned a lot on the go and the hard way, so it was easier for us to know what the things we needed to have in place were, but there were many things that needed to be in place. It was really a collaborative effort. The adult bone marrow transplant service, the pediatric bone marrow transplant service were involved, our stem cell processing and collection who were going to collect the T-cells were involved, we had members from the neuro-oncology service, from the emergency room, from the intensive care unit, who all had to be trained to understand the toxicities of these therapies and to deliver treatment to the patients because immediate treatment is actually crucial for their success and for management of the toxicities.

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Gore Treatment for the complications you mean?

22:36.400 --> 23:19.800

Isufi Treatment for the complications. So, it was not so much the chemotherapy aspect of it or the delivery of the T-cells we were familiar at doing that because we already a center that provides stem cell transplants for patients, but it was really managing the complications and having all the resources in place to be able to do it safely. Information technology was very actively involved in placing all the order sets in the computer. I mean, really, really it was anyone who was going to put their hands on the patient was trained.

23:19.800 --> 23:23.500

Gore Wow! So, I do not know, you must have been kind of nervous when the first patient was treated?

[23:23.500 --> 24:06.800](#)

Isufi We were. We were certainly normal, it is certainly normal to be nervous, again we had gone to many meetings, I had previously had other patients who had had this therapy at other institutions, I had taken care of them afterwards, but certainly it was when that first patient entered the hospital, certainly there was a pause and we were all anxiously waiting to see if they would respond to treatment from once and also what side effects they would have and if we were going to be able to manage them successfully.

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Gore And how did it work out if I can ask?

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Isufi It actually worked out great. It worked out great, the patients, the first couple of patients we treated went into remission and they did have some expected toxicities, but they were able to recover from them. They required treatments, again they required different subspecialists evaluating them, but they did very well. So, it was very hopeful, very exciting for them and for us, and we hope to have some support groups started for CAR-T cell therapy where they can share their experience with other patients as well. Because it is a scary process to go through for anyone. When you hear about these toxicities, it is understandable.

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Gore Absolutely. So, have you gotten involved with any research outside of these approved products?

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Isufi Yes. I am very happy to say that we have opened several clinical trials in lymphoma, in multiple myeloma and breast cancer.

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Gore Breast cancer?

[25:20.400 --> 25:21.800](#)

Isufi Breast cancer.

25:21.800 --> 25:33.700

Gore Wow! How does that work? I mean, how do you approach that. I mean, breast cancer seems like there are so many different types and very different than leukemia right?

25:33.700 --> 26:31.600

Isufi Exactly, and the challenge with breast cancer and other solid organ cancers is that these targets are not sitting on the cell surface like they are with leukemia and lymphoma. The targets for the T-cells, the majority of them, are inside the cells. But we do have antibodies that are approved in breast cancer that can actually go in and find the tumor cells and attack them, and what we have been able to do is have the T-cells bind to the antibodies that are binding to the cancer cells. And it is very similar, it is very similar to the standard CAR-T cell therapy but the genetically modified T-cell is not necessarily binding to the target on the cancer, it is binding to an antibody that binds the cancer cell.

26:31.600 --> 26:36.800

Gore And the antibody just to be clear that is binding to the cancer cell is a drug that has also been given.

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Isufi It is actually a drug that is part of routine care for breast cancer. It is a drug called Herceptin that recognizes HER2 on the cancer cells and the clinical trial specifically involves a genetically modified T-cell that has the ability to bind Herceptin.

27:00.000--> 27:11.800

Gore So, you give the patients Herceptin, which hopefully binds to their cancer cells and then you give these CAR-T that then bind to the Herceptin molecule and then it attacks the cancer cells presumably?

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Isufi Exactly. And what you get is the benefit of having millions of these T-cells go to the tumor and recognize the tumor cells way more than a patient who normally have circulating in their blood stream and reaching the tumor.

[27:32.700 --> 27:38.400](#)

Gore And these patients presumably may also be at risk for some of the side effects you described?

27:38.400 --> 28:27.500

Isufi Yes, certainly. And they are at risk for cytokine release syndrome, they are risk for neurologic toxicity and they also need to be monitored for other potential toxicities because we know that HER2 for example is not necessarily only found in cancer cells. The problem we run into is that for solid tumors, a lot of these targets are also found on normal tissue. So, lot of effort is going on, a lot of research is going and efforts are being made to find ways where the T-cells recognize the cancer cell without causing problems with the normal cells.

28:27.500 --> 28:33.400

Gore Well, that is really fascinating and I guess that is just a little taste of what is to come?

28:33.400 --> 28:53.400

Isufi Yes. It is very exciting. Now, scientists are developing cells, T-cells, that are genetically modified to actually be able to have on and off switches so that we can control the tumor, but we also have a handle and turn them off when we think that they have caused too much toxicity.

28:53.400 --> 28:58.400

Gore It is like the new faucets in your shower where you can set it for just right, not too hot.

28:58.400 --> 29:00.600

Isufi not too hot, not too cold exactly.

29:00.600 --> 29:02.900

Gore The Goldilocks, CAR-T cells.

[29:02.900 -->29:17.200](#)

Isufi Exactly. I mean just finding that sweet spot is actually the challenge right now. Fine tuning it where we get the most benefit against the tumor and we have the least toxicity.

29:17.200 --> 29:41.500

Dr. Iris Isufi is an Assistant Professor of Medicine at the Yale School of Medicine. If you have questions, the address is canceranswers@yale.edu and past editions of the program are available in audio and written form at YaleCancerCenter.org. We hope you will join us next week to learn more about the fight against cancer here on Connecticut Public Radio.