Funding for Yale Cancer Answers is provided by Smilow Cancer Hospital.

Welcome to Yale Cancer Answers with Doctor Anees Chagpar.

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’s a conversation about hematopathology and breast cancer research with Doctor Samuel Katz.

Dr. Katz is an associate professor of pathology at the Yale School of Medicine, where Doctor Chagpar is a professor.
So Dr. Katz, maybe we can start off by you telling us a little bit more about yourself and what it is you do. I'm a physician scientist within the Department of Pathology. I split my time where I spend 20% on clinical service diagnosing blood cancers, leukemias, and lymphomas. But I spend the majority of my time running a basic research laboratory that focuses on questions of how cells die. And we approach it from two different standpoints. By the pathway within the cells that cause them to die.
but also by a pathway external to the cells and how we can kill them. Because if we can manipulate the ability to kill cells, that could help in many different diseases like cancers. Tell us a little bit more about how you came to work on breast cancer as a hematopathologist. You mentioned that in your clinical role, you really focus on blood cancers. So how do you get into the breast cancer world? As a hematopathologist who focuses on the blood and the blood system, I got very interested in a
particular cell type called a T cell. And T cells are important in our immune system to attack cells that have been infected with foreign agents. They’re able to recognize the cells as being infected and kill them. And people have realized that they have such incredible ability to kill those infected cells that perhaps we can usurp that ability in order to attack other cells like cancer cells. And so tell us more about how this kind of works in breast cancer and more about your research.
many other types of cancers, there are proteins that are on the surface of the cell that are not present in normal cells. And so we have devised a protein that we can add into the T cells called a CAR or chimeric antigen receptor, thus making a CAR T cell that can recognize this aberrant protein on the breast cancer cell and direct the T cells killing ability towards that breast cancer cell. That sounds really fascinating. So tell us more about how CAR T therapy works. I know some of our listeners
NOTE Confidence: 0.915714538571429
00:03:17.324 --> 00:03:18.760 may be familiar with this,
NOTE Confidence: 0.915714538571429
00:03:18.760 --> 00:03:21.020 but many may not be. So, you know,
NOTE Confidence: 0.915714538571429
00:03:21.020 --> 00:03:23.400 how do you actually change these T
NOTE Confidence: 0.915714538571429
00:03:23.479 --> 00:03:25.945 cells to make them recognize these
NOTE Confidence: 0.915714538571429
00:03:25.945 --> 00:03:28.520 proteins on the surface of the cell?
NOTE Confidence: 0.915714538571429
00:03:28.520 --> 00:03:29.965 Because it sounds like essentially
NOTE Confidence: 0.915714538571429
00:03:29.965 --> 00:03:31.410 what you’re doing is you’re
NOTE Confidence: 0.915714538571429
00:03:31.460 --> 00:03:33.000 taking a patient’s immune system,
NOTE Confidence: 0.915714538571429
00:03:33.000 --> 00:03:34.044 these T cells,
NOTE Confidence: 0.915714538571429
00:03:34.044 --> 00:03:36.848 and you’re kind of giving them a GPS, a
NOTE Confidence: 0.915714538571429
00:03:36.848 --> 00:03:39.792 targeting system to say go after those cells,
NOTE Confidence: 0.915714538571429
00:03:39.800 --> 00:03:40.892 those cancer cells,
NOTE Confidence: 0.915714538571429
00:03:40.892 --> 00:03:43.076 but somehow you have to get
NOTE Confidence: 0.915714538571429
00:03:43.076 --> 00:03:45.156 the GPS into those T cells.
NOTE Confidence: 0.915714538571429
00:03:45.160 --> 00:03:46.636 How do you do that exactly?
NOTE Confidence: 0.948618271818182
Absolutely. And so there's a number of ways in which to reprogram those T cells. The most commonly used ones are viral approaches using retroviruses or lentiviruses where a piece of DNA and that virus will infect the cell and then integrate or become part of that cell's genome or DNA. Another way in which to do it, which is the approach we've taken and really came about because of...
some work by a senior professor here at Yale called Sherman Weissman. He kind of took me under his wing as a mentor in this approach where instead of using DNA, he was using RNA. And so we can take the T cells out of the patient and what we call Electroplate in order to give them kind of a little shock that gets the RNA into the cells. And this has a very high efficiency of being able to reprogram those cells using the RNA in this manner. But it also has a lot of other advantages, chief among them being safety in that
when you put an RNA into a cell, it doesn’t change the genome of all of the T cells that you’re taking from the patients. It only makes that RNA which then makes that protein and after a period of time it goes away. And so there’s an added safety to that. The RNA actually is very short lived, but the protein it
makes can last a little longer and it really depends on the particular protein that you’re making. But we see it in the order of about a week or so. So one could envision giving this therapy as a weekly type of basis where you’re giving the cells that have been reprogrammed with RNA or in newer work that’s still ongoing trying to actually deliver the RNA into the body without having to take out the T cells to reprogram them. It sounds like it really is intriguing, right, that you kind of give these T cells a little shock,
00:06:35.200 --> 00:06:38.120 give them an RNA to make a protein.

00:06:38.120 --> 00:06:41.659 That protein, that CAR protein goes and attacks these cancer cells in a very specific way because presumably this protein is found on cancer cells and not on normal cells.

00:06:41.659 --> 00:06:44.592 So where are we in terms of actually getting this into clinical trials?

00:06:44.592 --> 00:06:46.912 There's a lot of work to be done to optimize the system overall and these include the things that improve the ability of the T cells to kill, to make sure that they don’t get exhausted.
to make sure that again, as we’re saying, to really make sure that it’s safe. We still have work to do in animal models before we can get it into the clinical sphere, but because of the RNA approach we do think it is a easier transition to getting it into patients. And in terms of the safety and side effects, can you talk a little bit more about the side effects? I mean I would assume that this has a lot to do with whether these
proteins are on normal cells in any capacity or whether they are really 100% only on cancer cells and also revving up the immune system. You may think that you might get some immune related side effects as these T cells go about doing their business. And these have been against actually targets that are on B cell malignancies or leukemias and lymphomas. And they’re going
after a target called CD 19, which is expressed on the surface of those B cells and that really is unique to those cancer cells as well as normal B cells. And so when the CAR T cells are introduced to those patients, it does get rid of all their normal B cells, but patients are fine with that. You can live without our B cells. There are some side effects that are seen with that therapy. One is a called a cytokine release syndrome where because you’re getting so much killing so quickly of the cancer, it releases a lot of the cytokines.
that leads to kind of like an immune storm within the patients. They feel very sick and you have to really watch them carefully within the hospital. And there’s also been some less well understood neurological disorders that occur in some patients. And some people have hypothesized that might be due to the fact that we’ve learned later that there’s a cell type within the brain that has very low expression of this target. And so then that gets us back to breast cancer and solid tumors where there aren’t as many great targets.
that we know of that are uniquely expressed on the surface of these cells.

The one that we’re going after actually turns out to be increased in more than half of triple negative breast cancers and its expression correlates with poor prognosis within these patients. There is some very low expression during development, but we have some reasons to believe that we can kind of thread the needle between this very high expression on the cancer and this perhaps low expression on some normal tissues. Yeah, I mean I think that in general for most cancer related drugs
It's never completely black and white. Even chemotherapy, we know we still use it really is designed to attack rapidly growing cells and dividing cells. But you still get some normal cells like your hair for example, which is why many patients undergoing chemotherapy lose their hair. So it sounds like even if there was a potential differential there, it still might be really handy in terms of a therapy, especially if it was less toxic than our standard therapies.
which for triple negative breast cancer are primarily chemotherapy.

Now the other question that I have for you is in triple negative breast cancer in particular, we've seen that there are now therapies that are being used that are immunotherapies. So really therapies that are designed to unleash the immune system especially because some of these triple negative breast cancers, they tend to evade the immune system. So if that's the case, and this CAR T therapy is really designed to use the immune system, is it the idea that this would
00:12:04.874 --> 00:12:06.658 be paired with immunotherapies or
00:12:06.658 --> 00:12:09.076 are you thinking about a different
00:12:09.076 --> 00:12:10.960 way of attacking this?
00:12:11.520 --> 00:12:14.516 So I think there is a potential
00:12:14.516 --> 00:12:17.079 for testing the two together,
00:12:17.080 --> 00:12:19.294 but it is very different in
00:12:19.294 --> 00:12:21.600 the way these two different
00:12:21.600 --> 00:12:23.712 classes of immunotherapies work.
00:12:23.712 --> 00:12:26.880 So the ones that you’re referring
00:12:26.960 --> 00:12:29.625 to, so-called checkpoint inhibitors,
00:12:29.625 --> 00:12:35.054 these are ones that rely on new
00:12:35.054 --> 00:12:37.124 antigens that are made within
00:12:37.124 --> 00:12:39.706 the cancer cell that are mutant
00:12:39.706 --> 00:12:42.238 and specific to the cancer cells.
00:12:42.240 --> 00:12:45.160 And they really are unique.
The T cells use their native, their normal T cell receptors to recognize those. But there's a so-called break mechanism that prevents the T cell from killing and the immunocheckpoint inhibitors take away that break, the CAR that I've been talking about, these CAR T cells, this is a new protein that we've devised by taking pieces of various other parts of the T cell receptor and other antigen recognition domains and they recognize or we've designed this one to recognize a specific protein that's not mutated but wild type.
And this then activates the CAR T cell rather than stopping the brake. I’d say it’s more akin to pressing on the gas pedal when we have that specific protein. Well, we need to take a short break for a medical minute, but please stay tuned to learn more about the role of pathology and new research into a potential target for metastatic triple negative breast cancer with my guest, Doctor Sam Katz.

Support for Yale Cancer Answers comes from Smilow Cancer Hospital where their Prostate and Urologic Cancers program provides a multispecialty team
dedicated to managing the diagnosis, evaluation, and treatment of bladder cancer.
Smilowcancerhospital.org.
The American Cancer Society estimates that more than 65,000 Americans will be diagnosed with head and neck cancer this year, making up about 4% of all cancers diagnosed. When detected early, however, head and neck cancers are easily treated and highly curable. Clinical trials are currently underway at federally designated comprehensive cancer centers, such as Yale Cancer Center and Smilow Cancer Hospital.
to test innovative new treatments for head and neck cancers.

Yale Cancer Center was recently awarded grants from the National Institutes of Health to fund the Yale Head and Neck Cancer Specialized Program of Research Excellence, or SPORE, to address critical barriers to treatment of head and neck squamous cell carcinoma due to resistance to immune DNA damaging and targeted therapy.

More information is available at yalecancercenter.org.

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Welcome back to Yale Cancer Answers.
This is Dr. Anees Chagpar and I’m joined tonight by my guest, Dr. Samuel Katz. We’re talking about the role of pathology and some new research into CAR T cells, and now for a new indication which is how traditional immunotherapies, these checkpoint inhibitors which we now use in triple negative breast cancer. So Dr. Katz, I want to go back to something you were mentioning right before the break, which is how traditional immunotherapies, these checkpoint inhibitors which we now use in triple negative breast cancer really kind of get rid of...
a break as you phrased it in terms of T cell killing, right. Because we know that certain cancer cells, especially triple negative cancer cells, may kind of put a brake on those T cells to kill off these cancer cells. And so traditional immunotherapies will remove that brake T therapy is more like an accelerator finding a new target on these cells to attack cancer cells in a different way. So kind of like putting on an accelerator. My question is how do those two work together or is there an interplay?
Thinking about, you know, driving a car, if you step on the gas while you’re still got a brake on, it generally doesn’t work very well. Can you talk a little bit more about that? Absolutely. And I think that’s why, as you kind of suggested, the combination of this might be very useful. Because while if you’re just releasing your foot off the brake by using these checkpoint inhibitors, if you don’t have something driving, if there isn’t a mutant antigen for you to go after,
then the car won’t move forward,
NOTE Confidence: 0.96799754666667
the T cell won’t kill.
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On the other hand, like you said,
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if the CAR T cell is engineered so that it
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is always pressing on the gas pedal yet,
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it might try going forward.
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But if you have that brake
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present at the same time,
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then it’s it won’t be able to.
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But if you can manipulate the
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cell in ways that many people
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are, to kind of combine the two,
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then perhaps we could get
NOTE Confidence: 0.96799754666667
the full benefit of this.
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I also want to bring up one other
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thing that you had
mentioned before the break,
which is kind of getting towards
the difference between solid
tumors like triple negative breast
cancer and the blood tumors where
CAR T’s have worked so well.
Solid tumors have remained a
real challenge for the CAR T field
to be able to work efficiently.
And that’s because they create
this tumor microenvironment that
kind of quells the T cell,
some of which might be to increase the
brake like we’ve been talking about.
Another way is you can imagine that
the car won't do so well if you’re always pressing the gas pedal right.

You’ll run out of gas eventually.

And a lot of the CAR T designs in the past have this problem where you’re always pushing on the gas even when you’re not, when you don’t want it to, when you don’t have that target in sight.

Fortunately, some work in the lab by Po Han Chen, another physician scientist who’s been working on this problem, came up with a new design towards our car to make it so that it only presses on the gas when we want it to.
That’s interesting.

Can you tell us a bit more about that?

I mean, one would think that if there wasn’t a target, the T cells really wouldn’t have anything to go after and so they would just be kind of floating around looking for that target if it should appear.

So how do you turn on and turn off these T cells so that they don’t get overly active and exhausted as you put it?

Yeah, that’s a great question.

And I think what we have to remember
is when we’re putting in this car,

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this chimeric antigen receptor,

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it’s really a man made

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Frankenstein type molecule.

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It hasn’t been engineered by nature over

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you know millions of years of evolution.

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It’s something that we’ve come up with

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and made in the lab and so therefore

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it doesn’t work necessarily perfectly.

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We’ve taken snippets of different

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proteins and put them together and a

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normal receptor that’s on the cell will

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only single to have its downstream

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effects when it engages its target.

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But these

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CARs that we’ve made ourselves,
they have a little leakiness to them, many of them. And that leads to what we call tonic singling, singling all the time or pressing on that gas pedal all the time. And Po Han has realized that one of those domains could be optimized to help reduce that issue. And I think that’s going to be really critical for when we start targeting solid tumors. And so when you say optimized, do you mean like it’s kind of got a way that it it learns when to
00:20:46.706 --> 00:20:48.477 turn on and when to turn off?
NOTE Confidence: 0.836603688333333
00:20:48.480 --> 00:20:50.930 Because presumably you want the thing to
NOTE Confidence: 0.836603688333333
00:20:50.930 --> 00:20:53.838 to turn on when there is that target,
NOTE Confidence: 0.836603688333333
00:20:53.840 --> 00:20:55.744 and you want it to go full speed
NOTE Confidence: 0.836603688333333
00:20:55.744 --> 00:20:57.240 ahead and kill that target.
NOTE Confidence: 0.836603688333333
00:20:57.240 --> 00:20:58.596 And when the target isn’t there,
NOTE Confidence: 0.836603688333333
00:20:58.600 --> 00:21:00.210 well, then you want it to conserve
NOTE Confidence: 0.836603688333333
00:21:00.210 --> 00:21:01.798 its energy and lay low for a bit?
NOTE Confidence: 0.964970972
00:21:02.440 --> 00:21:06.096 So looking at the actual structure
NOTE Confidence: 0.964970972
00:21:06.096 --> 00:21:10.352 or the presumed structure of the molecule,
NOTE Confidence: 0.964970972
00:21:10.360 --> 00:21:13.904 we hypothesized that they
NOTE Confidence: 0.964970972
00:21:13.904 --> 00:21:16.378 might be coming together.
NOTE Confidence: 0.964970972
00:21:16.378 --> 00:21:18.123 So the singling usually occurs
NOTE Confidence: 0.964970972
00:21:18.123 --> 00:21:20.515 when you get more than one of
NOTE Confidence: 0.964970972
00:21:20.515 --> 00:21:21.795 these CARs coming together,
NOTE Confidence: 0.964970972
00:21:21.800 --> 00:21:23.720 being brought together and that’s
what happens when it engages its target on the other cells. And so by changing one of those domains that we thought was leading to that aggregation and that baseline single, we were able to decrease that baseline singling and make it so that it only signals when it really is being brought together by the antigen on the other cell and not when it’s existing on its own in the T cell. The other question that I have for you is you mentioned that one of the things that makes solid tumors tricky is this tumor microenvironment.
the cancers know how to make an environment around themselves that’s very comfortable for the cancer cells to grow in and not so comfortable for anything else to kill them. But in thinking about CAR T therapy and blood cancers, you know when you think about metastatic disease, really there is potentially a way to think about solid tumors that maybe like a blood tumor in the sense that when they’re metastatic you’re really trying to get at the circulating tumor cells and
the disease that isn’t necessarily in a particular solid organ.

Can you talk a little bit about that, is CAR T therapy particularly good for metastatic disease and reducing the circulating tumor burden? Yeah, absolutely. So as I was mentioning the CD 19 CAR that targets B cell leukemias, that one works phenomenal. It doesn’t have any of the tonic singling that we were just talking about it is a great target. It’s all in the bloodstream and patients do very well with that. Just underneath that there are so-called
B cell lymphomas which take up residence. They form more of a mass as opposed to just being circulating through the bloodstream that they also can use the CD19 CAR and they do OK, not as well as the leukemias with that CD19 CAR, but still somewhat OK and part of that is probably this tumor microenvironment that’s created there. Now one of the best reasons to use the T cell to deliver these CAR T cells is that the T cells seek out and destroy these metastases throughout the body. There are molecules that kind of
tell them to look within these areas and it gets them places where other less smart drugs might not realize how to get to or where to go. And so improving CAR T cells ability to find these metastases is another active area of investigation. In fact, we have a collaboration with another senior professor John Morrow in determining ways of how we can improve the T cells ability to traffic to get to where they’re going. And then once they’re there, they have to then face this.
kind of a barrier, this impenetrable barrier that the tumor kind of forms this wall. And so there are other ways that people are designing to equip the T cells to kind of get through that barrier a little better. You know as you mentioned thinking about metastatic sites and so on and the ability for T cells potentially to navigate through these barriers better than other drugs. It makes you think about things that have been historically very difficult for us to treat with standard chemotherapy and that’s kind
00:25:18.162 --> 00:25:20.466 of getting to brain metastases and
NOTE Confidence: 0.904436884
00:25:20.466 --> 00:25:22.680 getting past the blood brain barrier.
NOTE Confidence: 0.904436884
00:25:22.680 --> 00:25:24.480 But earlier before the break,
NOTE Confidence: 0.904436884
00:25:24.480 --> 00:25:28.500 you were talking about some neurotoxicity
NOTE Confidence: 0.904436884
00:25:28.500 --> 00:25:30.932 associated with these newer therapies.
NOTE Confidence: 0.904436884
00:25:30.932 --> 00:25:33.116 Can you talk a little bit
NOTE Confidence: 0.904436884
00:25:33.116 --> 00:25:35.038 about whether CAR T therapy,
NOTE Confidence: 0.904436884
00:25:35.040 --> 00:25:37.158 you envisage this really having a
NOTE Confidence: 0.904436884
00:25:37.158 --> 00:25:39.896 role to play in in brain metastases
NOTE Confidence: 0.904436884
00:25:39.896 --> 00:25:42.392 and how exactly that would work?
NOTE Confidence: 0.957833628
00:25:42.960 --> 00:25:46.240 Yeah, absolutely. So interestingly enough,
NOTE Confidence: 0.957833628
00:25:46.240 --> 00:25:49.624 some of those original patients that
NOTE Confidence: 0.957833628
00:25:49.624 --> 00:25:52.568 had leukemias or blood lymphomas wound
NOTE Confidence: 0.957833628
00:25:52.568 --> 00:25:55.064 up having disease within their brain
NOTE Confidence: 0.957833628
00:25:55.064 --> 00:25:57.971 and it was found that the CAR T cells
NOTE Confidence: 0.957833628
were making were actually fighting off the disease that was there. So I think the potential is possible and it’s not quite understood yet whether they were able to get in because the blood brain barrier that we talked about was disrupted a little bit because the disease was already there or whether the CAR T cells are able to even in a completely intact blood vein barrier get in. But I think there’s certainly is the potential and there have been several studies since then trying to target not just hematopoietic tumors that make it to the brain,
but also solid tumors that have made it to the brain as well.

In addition to brain tumors themselves, where there are different CARs that people have been developing in order to do that. And there is some evidence of some efficacy still needs to be improved though.

Yeah, you know the, it sounds like such a wonderful exciting new target, but I wonder about the downsides as well. So you know when we think about really turning on the immune system after having lived through the the COVID pandemic, many of us saw that there were some patients whose immune systems were turned.
on so much that you ended up with this immune storm and really that caused a lot of side effects for these patients. Would you expect the same kind of thing with CAR T therapy? I mean, it seems like it might be a balance between too much and too little. On the one hand, you don’t want your T cells to get exhausted. On the other hand, you don’t want them working too hard either, at the expense of toxicity. Absolutely. And this is one of the reasons why I really appreciate the wisdom of Sherman Weissman in devising this RNA approach.
So when you give a standard CAR therapy using the lentiviral type approach and DNA, you really don’t have any control over those T cells and how much they proliferate, how long they stay around for, what kind of dosing you give. And if a patient winds up having some of these side effects, there’s not much you can do. On the other hand, for the RNA approach, you can very precisely decide how much you’re giving and when, and you can titrate that amount so that you can make it less if in order.
to not get into that territory where you get those types of side effects.

Samuel Katz is an associate professor of pathology at the Yale School of Medicine.

If you have questions, the address is canceranswers@yale.edu, and past additions of the program are available in audio and written form at yalecancercenter.org.

We hope you’ll join us next time to learn more about the fight against cancer. Funding for Yale Cancer Answers is provided by Smilow Cancer Hospital.