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Welcome to Yale Cancer Answers with your host 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 Melanoma research with doctor Jeffrey Ishizuka.

Doctor Ishizuka is an Assistant Professor of Medical Oncology at Yale School of Medicine, where Doctor Chagpar is a Professor of Surgical Oncology.

Jeff, maybe we could start off by you telling us a little bit about yourself and what you do.

I’m a physician-scientist and that means that I spend part of my time treating cancer patients and part of my time in the lab looking for new treatments for those patients.

And so tell us a little bit more about the kinds of patients that you treat and the kinds of research that you do.

I see Melanoma patients and I’m an immunologist by training. And that means I study ways to make the patient’s immune system work better, to attack the cancer.

Tell us more about that, we’ve talked on the show a little bit about immunotherapy and so on,

but tell us a little bit more about the broad spectrum of immunotherapy.

How exactly does it work and then the role that it plays in Melanoma.

There are a couple of types of immunotherapy.

And for a long time we knew that the immune system had the potential to control cancer,
but I’d say the two big advances that are more recent are on the one hand,

CAR T cells. And those are cells that are taken out of the patients’ body and reprogrammed to go back in and attack the tumor, and immune checkpoint blockade. And these are drugs that cut the brakes on the immune system.

Those brakes stop the immune system from attacking the cancer. And when you get rid of them, the cancer is vulnerable to immune attack. Tell us about which of these you work on, and how exactly they work in Melanoma.

In Melanoma, immune checkpoint blockade has really been one of the biggest developments really in the last, well maybe ever in the disease. And I think Melanoma was the first disease where these drugs were developed and remains one of the ones where they work the best.

Can you talk about this immune checkpoint blockade. Is there more than one molecule that needs to be blocked?

How does that work? Why does the immune system have brakes to begin with? These are great questions and they’re really at the forefront of the field right now, so there are certainly at least a few molecules that are important.

And all of the ones we learned about first are on the surface of T cells, which we know are one of the important cells for controlling cancer. There are a number of molecules that target PD-L1 and that’s a major inhibitory pathway in the T cells, and also molecules that target CTL A4,
which is another inhibitory pathway in T cells. And what we learned is when you block either one of these and sometimes if you block them both together it works even better. The T cells can get supercharged to attack the cancer.

Why is it that they have breaks to begin with?

The immune system is supposed to be able to identify foreign stuff in our bodies and get rid of it.

So why doesn’t that work in cancer?

Why is it that we need to take off these brakes?

Why do they have breaks to begin with?

This is the foundational question of immunology, the distinction between self and nonself.

All cells need to be able to get rid of foreign things just as you said,

but at the same time they need to have mechanisms to avoid attacking the normal cells in the body that are healthy and so why is it that the immune system thinks that these cancer cells are normal?

I think it’s really because cancer cells arise from normal cells as normal cells become dysregulated as they acquire genetic errors called mutations.

And eventually you develop cancer.

And because the cancer cell arises from a backdrop of normal cells,

doing normal cell things, the immune system has to find specific signals of damage or mutations that look abnormal in order to recognize cancer.

So you’re telling me that normally it won’t do that?

Some tumors are recognized by the immune system and the immune system can actually get rid of them,

and other aren’t. And really what we’re trying to understand and at the heart of the field is how can we take tumors that are not well recognized by
0:05:02.615 –> 0:05:07.141 the immune system and turn them into tumors that the immune system can see and destroy?

0:05:07.141 –> 0:05:10.75 And so it seems to me that if you take that problem just at its face,

0:05:10.75 –> 0:05:13.264 there are two ways of doing that.

0:05:13.264 –> 0:05:18.617 One is to make the tumor look more abnormal so that the immune system

0:05:18.617 –> 0:05:27.904 realizes, I need to attack it and get rid of it without actually revving up the immune system or getting rid of the

0:05:27.904 –> 0:05:36.675 brakes and the other is to supercharge the immune system as you put it to make it more sensitive to recognizing what might be abnormal.

0:05:36.675 –> 0:05:41.899 Yeah, that’s right, and I think people are working at both sides of that problem.

0:05:41.899 –> 0:05:49.271 We and others in the lab, are thinking of strategies both to make tumors put out signs for the immune system, saying,

0:05:49.271 –> 0:05:55.995 come get me and also looking for new ways to charge the immune system to be more aggressive against cancer.

0:05:55.995 –> 0:05:57.94 Tell us more about the first,

0:05:57.94 –> 0:06:04.721 because I think that we’ve heard a little bit about checkpoint inhibitors,

0:06:04.721 –> 0:06:11.267 but we really haven’t heard a lot about the work that’s going on to have tumor cells put out those signs that

0:06:11.267 –> 0:06:22.262 say, come get me. And it seems to me that might be a way to allow the immune system without getting supercharged to eat up or

0:06:22.262 –> 0:06:24.663 get rid of these cancer cells,

0:06:24.663 –> 0:06:26.91 because one of the problems,

0:06:26.91 –> 0:06:35.04 as you point out, of having a supercharged immune system is that it can then attack its own cells.

0:06:35.04 –> 0:06:37.966 Yeah, that’s a great point and

0:06:37.966 –> 0:06:42.72 we’ve been thinking, and others as well,

0:06:42.72 –> 0:06:49.041 that it comes down to tricking the tumor cell into making inflammatory signals,

0:06:49.041 –> 0:06:56.002 tricking it into making kind of an antiviral response that recruits anti tumor immune cells into the micro environment,

0:06:56.002 –> 0:06:57.336 and I think
you can go about that by infecting the tumor with a virus or making it think it’s infected with a virus or triggering certain danger signals in the micro environment directly around the tumor.

Tell us more about that work, is that actually something that’s being done? Is it in clinical practice?

How do we do that?

There are a number of clinical trials now using stimulators of viral pathways that look like DNA or RNA, things that viruses make and that ourselves have dedicated sensors in order to detect, and I think none of them has proven to be the Magic bullet for cancer yet. But there are still some technical hurdles to workout. And I think we’re getting there though. Why has that not proven to be as successful as supercharging the immune system?

I think one of the challenges is that cancer in many cases can spread to many locations, and when you think about triggering an inflammatory response in the tumor bed, you’re really thinking about triggering it, not just at one site, but at many sites all at once, and so finding ways to send drugs to all of the different sites that cancer occupies in the body is one of the major challenges to getting this approach to work. The other approach then is the one that is the mainstay of immunotherapy, which is to quote supercharge the immune system to get rid of the blocks. I always think of it like Harry Potter’s invisibility cloak, right. The tumor has kind of made itself invisible to the immune system,
0:08:48.403 –> 0:08:57.1 and it’s getting rid of that that cloak and getting the immune system to recognize it and to go after it and two,

0:08:57.1 –> 0:08:59.63 to be quote supercharged now.

0:08:59.63 –> 0:09:09.755 You mentioned two molecules, in particular CTL A4 and PDL1, tell us a little bit about the differences between the two.

0:09:09.755 –> 0:09:14.227 I mean we have drugs that will block either pathway.

0:09:14.227 –> 0:09:17.602 How do you figure out which one to use?

0:09:17.602 –> 0:09:20.556 Tell us more about that interplay.

0:09:20.556 –> 0:09:29.019 I think we still don’t fully understand the mechanism of either drug and either pathway.

0:09:29.019 –> 0:09:32.062 And people have done a lot of good work,

0:09:32.062 –> 0:09:36.102 in fact, the Nobel Prize was awarded a few years back for some of that work,

0:09:36.102 –> 0:09:39.042 but I wouldn’t say that we completely understand which,

0:09:39.042 –> 0:09:41.508 even sometimes which cells are being targeted,

0:09:41.508 –> 0:09:44.918 but certainly which pathways within the cell are being activated.

0:09:44.918 –> 0:09:47.961 So a lot of how we figured this out has been empirically.

0:09:47.961 –> 0:09:52.369 We’ve done clinical trials with different drugs or different combinations of drugs,

0:09:52.369 –> 0:09:55.044 and we’ve seen what’s been effective for patients,

0:09:55.044 –> 0:09:59.085 and the hope is going forward that as we learn more about the immune system,

0:09:59.085 –> 0:10:04.15 and as we learn more about the tumor that we will be able to do better

0:10:04.15 –> 0:10:09.876 and even predict the next set of these drugs that could be usefully combined.

0:10:09.876 –> 0:10:14.153 So tell us more about the differences between CTLA for an PDL1.

0:10:14.153 –> 0:10:24.486 I get the fact that we’ve discovered these kind of fortuitously and empirically and have just made drugs that affect each of these pathways,

0:10:24.486 –> 0:10:26.264 and seeing that they work.

0:10:26.264 –> 0:10:29.62 But we must know more about these actual molecules.
Yeah, they both play an inhibitory role in T cells. I think it’s broadly thought that one of them plays more of a role in T cells initially getting primed against the tumor, but maybe plays more of a role in lymph nodes then generating the T cells that are capable of responding whereas the other one, that speedy one may play more of a role in activating the T cells that are already primed against the tumor that already have the capacity to attack the tumor. And I’m going to steer clear of the term of exhaustion because there are a lot of debates about whether T cells are actually exhausted or not, but there’s this idea that T cells can, after seeing a lot of tumor antigen stop responding very well that they can become dysfunctional and so one of the things that PDL1 blockade does, is to make the T cells that have become dysfunctional more functional. And so if these two pathways then are complementary, one being more so for priming T cells and one being more so for T cells that are already primed, has there been any work looking into either concurrent therapy or sequential therapy of different immuno therapies that might work better than either in isolation? There has, and in Melanoma combining two drugs, one that targets CTL A4, and one that targets PDL1 seems to be better than using either drug alone and potentially better than using them both in sequence, although the latter is a less clear conclusion. And one of the exciting things in this field has been seeing the slew of approvals for immuno therapies in different cancer types in Melanoma. Certainly it’s become standard of care in the frontline for most patients and it’s being explored in basically every stage of care of the disease other than for disease that can just be removed and surgically cut out in the early stages and really beyond Melanoma.
It spread throughout many solid tumor types and it’s being tried in almost any tumor type you can think of.

And so two questions. First question is one of the things you mentioned earlier as being one of the downfalls of some therapies is that it can’t always get to all of the cells where the tumors may be hiding.

Does immunotherapy have that problem in terms of getting to the T cells and activating them or supercharging them?

Or is that concept, this may not work if there’s a tumor, for example in the brain? Because this drug can’t cross the blood brain barrier?

We know that we can get effects certainly in the brain.

So you can see effects of these drugs in what are thought of usually as sites of the body that are hard to get to or immune privilege sites but I guess what I don’t know for sure, it’s hard to say is whether there is a problem activating immune cells somewhere in the body.

That is to say, whether we’re getting these drugs as effectively as possible to all the immune cells that might be able to be mobilize against the tumor.

We’re going to learn a lot more about Melanoma immunotherapy right after we take a short break for a medical minute.

Please stay tuned to learn more about this research with my guest doctor Jeffrey Ishizuka. Support for Yale Cancer Answers comes from AstraZeneca.

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You’re listening to Connecticut public radio.
Welcome back to Yale Cancer Answers.
This is doctor Anees Chagpar and I’m joined tonight by my guest doctor Jeffrey Ishizuka.
We’re talking about Melanoma research and in particular we’re talking about immunotherapy.
Jeff, right before the break we were talking a little bit about immunotherapy in terms of,
really getting the immune system to attack cancer cells,
which it may not recognize because as you put it,
these cancer cells come from normal cells and that may not be as foreign looking to the immune system to really trigger it and we talked a little bit about two separate pathways,
CTL A4 and PDL1 and the fact that we now have drugs,
this explosion of drugs in immunotherapy targeting these two pathways and how this really has become the mainstay of therapy,
particularly for cancers like Melanoma.
I had a few questions to kind of follow up on that.
The first is, tell us a little bit about the side effects.
We think about chemotherapy, and you know, traditionally, chemotherapy was therapy that kills off cancer cells and was really thought to be therapy that switches off rapidly dividing cells and so people ended up losing hair and maybe getting sick because it effects your GI lining, which are rapidly turning over cells.

Do you get the same kind of thing in immunotherapy, or are there other side effects that are the results of kind of supercharging this immune system and getting the immune system to attack healthy cells?

So I think that’s it exactly.

Many of the side effects that you get from immunotherapy are actually side effects of supercharging the immune system, so the immune system can accidentally attack different areas of the body.

Some of the things we see are inflammation in the lungs, inflammation in the GI system we see inflammation of the endocrine system, and when we first started seeing these side effects, there wasn’t a good sense of how you treat them, how you manage them, or even how you monitor.

We didn’t really know what to look for.

But I will say that as experience with these agents has progressed, we’ve gotten better at detecting these side effects as they occur, and managing them, usually using immunosuppressives and one of the questions that comes up when you start saying, well, you’re using drugs to charge the immune system and at the same time to shut down the immune system, is that going to be is going to be bad for the patients.

Are they going to have that outcomes and the data isn’t really completely mature on this yet,
but it certainly appears from the early data that you can safely give these immunosuppressives and that you don’t at least don’t clearly make their responses against the cancer worse.

That’s really interesting. Why would that be the case? I can imagine that when we think about people who are immunosuppressed, people who for example have HIV or other things that turn off their immune system, they are more at risk of developing cancer, and I guess for the same reason that you talked about before the break, which is your immune system, unbeknownst to you, might be getting rid of little cancers that you don’t know you have because it recognizes them and it gets rid of them, and so if you are immuno compromised you’re at increased risk of getting cancer, and that’s the whole point of supercharging the immune system to get rid of these cancers.

Why is it that giving people an immunosuppressant at the same time as an immuno supercharger doesn’t seem to affect the cancer in a bad way? A couple of potential thoughts here. The first one is that I want to be careful we don’t know for sure that it doesn’t affect the response to therapy in a negative way. I think what we can say is that at first blush, patients who needed immunosuppressives because they had these bad immune effects and got them didn’t do obviously worse, at least in the early studies. Then patients who didn’t need them in the first place and that actually could be a kind of selection bias issue where the patients who needed the immunosuppressives
actually were having the strongest immune responses to begin with,
and so I think we have to do some careful experiments in a controlled setting to see whether it was really true that the immunosuppressives weren’t having any effect there.
And I think that’s probably the main thing that I would think about for that issue.
The other question that I have is, these autoimmune side effects, the side effects of people’s immune system now attacking their own normal cells,
are those permanent? Are they forever or are they short lived? I mean when you get chemotherapy and you lose your hair,
your hair will grow back. Is it the same with immunotherapy that this is a short term thing?
Or when your immune system attacks your lungs, now you’ve got pulmonary fibrosis forever?
I think it depends on the type of immune side effect that we’re talking about.
I think many of them, if they’re controlled with immunosuppressives,
and if you take the patient off of the immunotherapy, will actually go away.
So we see this in a lot of cases, inflammation in the colon, or inflammation in the lungs.
I think the case in which this isn’t necessarily true is when the immune system attacks the cell type
that produces hormones in the body and destroys all of that cell type because in that case you may not really know what’s going on until the cell type
is gone, and after that there’s really no bringing it back.
So in most cases we actually have been able to give hormone replacement. It’s extremely bad if it’s not detected, but in a lot of cases it can be solved by giving a pill a day. When you talk about hormones, are you talking about thyroid are you talking about ovaries, what hormones are we talking about? Yeah, so thyroid is one that you certainly see, but you see actually a number of other hormones that are produced in the brain that can also be altered, and these can be more rare, but can be pretty dramatic if you see them. So given the side effects of immunotherapy, is immunotherapy really better than classic chemotherapy? You had mentioned that immunotherapy has now become standard of care for Melanoma. Is it better than what we used to do? We used to give chemotherapy for Melanoma, right? And Melanoma is not particularly responsive to chemotherapy, I think what excited everyone in the field and it’s given us all a lot of excitement and a lot of hope is not even that everyone responds to these immunotherapy’s because they don’t, not enough patients do, and that’s something we don’t really understand. We’re trying to understand it in the lab, but it’s that some of the patients who respond seem to just keep responding, and some of them respond so well and for so long that we’ve actually started to believe that we can take the patients off of the drugs,
the immunotherapy drugs, and that the cancer won’t return. And this is true even in some cases for very aggressive disease. And so seeing those effects are the ones that have really made everybody excited. And you see that in clinical trials when we study how patients survive on different drugs and it was no contest between the immunotherapy’s and chemotherapy. When we talk about therapy for cancer a lot of times we’re talking about personalized medicine and we’re talking about how we can figure out what a cancer likes to eat, what receptors cancer has, what genes are turned on and turned off, and then we target our therapy accordingly. Talk about immunotherapy. It seems to me like we’re talking about a blanket turning on supercharging the immune system, is that right, or are there ways where we’re actually tailoring this therapy? Are we looking at who those people are that are super responsive to immunotherapy versus the people who are not super responsive to immunotherapy? Yeah, so this question is near and dear to my heart. We in general don’t do a great job of selecting patients to get particular immunotherapy, there is one biomarker which is the expression of PDL1 in the tumor as we talked about PDL1 and PD1 is one of these key pathways, so if you have PDL1 expressed in the tumor microenvironment either by immune cells in the micro environment or by the tumor, we know that you are more likely to have a response to targeting the PD1 PDL1 axis.
But basically everyone in the field spends a lot of time complaining about this biomarker because we know there are a lot of patients who will have PDL1 expression in their tumor who won’t respond well to these drugs. And conversely, there are a lot of patients who won’t have PDL1 expression in the tumor who will still respond to these drugs. So what’s the point of the biomarker then? We know it’s better than not using it in terms of you have some predictive value and in some cases you might not even be able to see a signal of the drug working in a patient population and unless, you used a biomarker, and also it’s a stand in because we haven’t done a good enough job yet of finding better ones. So we have this biomarker that if you have it, you won’t necessarily respond to the immunotherapy, if you don’t have it, you may still respond to the therapy, so either way you’re likely going to get immunotherapy if you have Melanoma, regardless of whether you have the biomarker or not. That’s true, and that’s where I think we have the potential to do much better, particularly as we talked about these two pathways, there are a lot of other immuno regulatory pathways that can activate immune cells or can activate the tumor to recruit immune cells. And we’re still at the beginning of understanding these.

But as these drugs come out and as they are available we have the potential to start thinking about OK for a given patient. How can we assess that patients immune system and how can we understand the tumor, the genomics, the genetics of the tumor in such a way that we can find the best combination of drugs to work for that patient. That sounds really interesting,
because that sounds like the stuff that we’ve been doing for awhile now in terms of cancer and looking at cancers in figuring out which therapy is going to work better. What targeted pathways are turned on versus turned off.

Should you be using, you know an anti HER-2 agent in somebody who’s got a HER-2-positive breast cancer? Or should you be targeting KRAS in lung cancer? Sounds like you’re moving in the same direction in Melanoma.

But looking at it from an immune perspective, and I should say this is mostly on the research side, right now we’re trying to understand the flavors of inflammation in the tumor microenvironment. The composition of the immune cells that are there and why they’re there, and then once we understand that, we’re simultaneously starting to look at OK if we take pieces of the tumor and study them in tissue culture, if we study them in a dish and treat them with different immunotherapy drugs, can we see patterns of response from some patients but not from others? Those are things that we’re working on here, and others are working on as well that we think could lead to the development of better biomarkers. That’s one kind of major approach.

Another one is focusing on the technologies that have emerged to sequence patient genomes. The immune cells from patient genomes. We do technologies now to look at individual cells in sequence. Everything that that cell is expressing. Basically everything it’s doing and we can do that for a bunch of cells in the micro environment all at once, and the thought is that we may find particular genetic lesions in the tumor that lead to a better response to immunotherapy A versus B.
We may find particular features of the immune system that interact with the tumor as well that predict that, and so I think that in the next 5 or 10 years we’re likely to see progress in this direction. Whether that will translate affectively into guiding precise therapy choice for a patients Melanoma, I’m not sure. When you talk about, essentially taking tumors and looking at the micro environment and seeing the composition of these cancer cells, you can also look at the immune system and see, maybe my immune system is different from your immune system in terms of attacking a particular cell. Is that on the right track? It’s exactly on the right track, and you know, even taking a step back when we first started to see that these therapies could work for patients, people started to ask, why do they work for some patients but not for others? And we started to look inside patient tumors and one of the things that was clear is that some patients have a lot of attacking immune cells even prior to immunotherapy and others don’t. And just unpacking that basic observation is something we’re still doing, as we start to understand it as we start to understand the chemical signals that the tumor in the immune system makes. It’s giving us a lot of inputs to try to determine which drugs could be affective in each case, and what the basic flavors of immune micro environment are.
Doctor Jeffrey Ishizuka is an Assistant Professor of Medical Oncology 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.

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