WEBVTT

- $1\ 00:00:00.000.000$ --> 00:00:03.822 Support for Yale Cancer Answers comes from AstraZeneca.
- 2~00:00:03.822 --> 00:00:14.170 the Beyond Pink campaign aims to empower metastatic breast cancer patients and their loved ones to learn more about their diagnosis and make informed decisions.
- $3\ 00:00:14.170 --> 00:00:17.879$ Learn more at lifebeyondpink.com.
- $4\,00:00:17.879 \longrightarrow 00:00:20.550$ Welcome to Yale Cancer Answers with your host
- 5~00:00:20.550 --> 00:00:21.969 Doctor Anees Chappar.
- 6~00:00:21.969 --> 00:00:31.855 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
- 7~00:00:31.855 --> 00:00:36.057 it's a conversation about Melanoma research with doctor Jeffrey Ishizuka.
- 800:00:36.057 --> 00:00:41.341 Doctor Ishizuka is an Assistant Professor of Medical Oncology at Yale School of Medicine,
- 9 00:00:41.341 --> 00:00:45.909 where Doctor Chagpar is a Professor of Surgical Oncology.
- $10\ 00:00:45.909 -> 00:00:51.234$ Jeff, maybe we could start off by you telling us a little bit about yourself and what you do.
- $11\ 00:00:51.234$ --> 00:00:59.524 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
- $12\ 00{:}00{:}59.524 \longrightarrow 00{:}01{:}02.189$ for new treatments for those patients.
- 13 00:01:02.189 --> 00:01:09.043 And so tell us a little bit more about the kinds of patients that you treat and the kinds of research that you do.
- $14\ 00:01:09.043 \dashrightarrow 00:01:12.381$ I see Melanoma patients and I'm an immunologist
- $15~00:01:12.381 \longrightarrow 00:01:15.956$ by training. And that means I study ways to
- $16\ 00:01:15.956 \longrightarrow 00:01:19.174$ make the patient's immune system work better,
- $17\ 00:01:19.174 \longrightarrow 00:01:22.153$ to attack the cancer.
- $18\ 00:01:22.153 \longrightarrow 00:01:26.861$ Tell us more about that, we've talked on the show a little bit about immunotherapy and so on,
- $19\ 00{:}01{:}26.861 --> 00{:}01{:}31.808$ but tell us a little bit more about the broad spectrum of immunotherapy.

- $20\ 00:01:31.808$ --> 00:01:35.575 How exactly does it work and then the role that it plays in Melanoma.
- 21 00:01:35.575 --> 00:01:38.382 There are a couple of types of immunotherapy.
- $22\ 00:01:38.382 \longrightarrow 00:01:43.078$ And for a long time we knew that the immune system had the potential to control cancer,
- $23\ 00:01:43.078 \longrightarrow 00:01:46.906$ but I'd say the two big advances that are more recent are on the one hand,
- $24\ 00:01:46.906 --> 00:01:54.662$ 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
- $25\ 00{:}01{:}54.662 \dashrightarrow 00{:}01{:}58.337$ blockade. And these are drugs that cut the brakes on the immune system.
- $26\ 00:01:58.337 \longrightarrow 00:02:02.114$ Those brakes stop the immune system from attacking the cancer.
- 27 00:02:02.114 --> 00:02:03.644 And when you get rid of them,
- $28\ 00:02:03.644 \longrightarrow 00:02:08.692$ the cancer is vulnerable to immune attack.
- 29 00:02:08.692 --> 00:02:12.393 Tell us about which of these you work on, and
- $30\ 00:02:12.393 \longrightarrow 00:02:15.500$ how exactly they work in Melanoma.
- $31\ 00:02:15.500 --> 00:02:22.020$ In Melanoma, immune checkpoint blockade has really been one of the biggest developments
- $32\ 00:02:22.020 \longrightarrow 00:02:26.522$ really in the last, well maybe ever in the disease.
- 33 00:02:26.522 --> 00:02:31.093 And I think Melanoma was the first disease where
- $34\ 00:02:31.093 --> 00:02:37.520$ these drugs were developed and remains one of the ones where they work the best.
- $36\ 00{:}02{:}38.639 \longrightarrow 00{:}02{:}41.776$ Can you talk about this immune checkpoint blockade.
- $37\ 00:02:41.776 --> 00:02:45.025$ Is there more than one molecule that needs to be blocked?
- $38\ 00:02:45.025 --> 00:02:49.169$ How does that work? Why does the immune system have brakes to begin with?
- $39\ 00:02:49.169 \longrightarrow 00:02:54.323$ These are great questions and they're really at the forefront of the field right now,
- $40\ 00:02:54.323 --> 00:02:58.132$ so there are certainly at least a few molecules that are important.

- $41\ 00:02:58.132 \longrightarrow 00:03:02.221$ And all of the ones we learned about first are on the surface of T cells,
- $42\ 00:03:02.221$ --> 00:03:07.205 which we know are one of the important cells for controlling cancer.
- $43\ 00:03:07.205 --> 00:03:09.669$ There are a number of molecules that target
- $44~00:03:09.669 \dots > 00:03:13.354$ PD-L1 and that's a major inhibitory pathway in the T cells,
- 45 00:03:13.354 --> 00:03:15.453 and also molecules that target CTL A4,
- $46\ 00:03:15.453 \longrightarrow 00:03:18.174$ which is another inhibitory pathway in T cells.
- $47~00:03:18.174 \longrightarrow 00:03:25.318$ And what we learned is when you block either one of these and sometimes if you block them both together it works even better.
- $48\ 00:03:25.318$ --> 00:03:28.378 The T cells can get supercharged to attack the cancer.
- 49 00:03:28.378 --> 00:03:30.039 Why is it that
- 50 00:03:30.039 --> 00:03:32.086 they have breaks to begin with?
- $51\ 00:03:32.086$ --> 00:03:38.991 The immune system is supposed to be able to identify foreign stuff in our bodies and get rid of it.
- 52 00:03:38.991 --> 00:03:41.996 So why doesn't that work in cancer?
- $53\ 00:03:41.996 \longrightarrow 00:03:45.128$ Why is it that we need to take off these brakes?
- $54\ 00:03:45.128 \longrightarrow 00:03:47.622$ Why do they have breaks to begin with?
- $55\ 00:03:47.622 \longrightarrow 00:03:51.651$ This is the foundational question of immunology,
- $56\ 00:03:51.651 \longrightarrow 00:03:54.527$ the distinction between self and nonself.
- $57\ 00:03:54.527 \longrightarrow 00:03:59.387$ All cells need to be able to get rid of foreign things just as you said,
- $58\ 00:03:59.387 \longrightarrow 00:04:00.729$ but at the same time
- $59\ 00:04:00.729$ --> 00:04:09.909 they need to have mechanisms to avoid attacking the normal cells in the body that are healthy and so
- $60\ 00:04:09.909 \longrightarrow 00:04:15.647$ why is it that the immune system thinks that these cancer cells are normal?
- $61\ 00:04:15.647$ --> $00:04:26.511\ I$ think it's really because cancer cells arise from normal cells as normal cells become dysregulated as they acquire genetic errors called mutations.
- 62 00:04:26.511 --> 00:04:29.175 And eventually you develop cancer.

- $63\ 00:04:29.175 --> 00:04:33.819$ And because the cancer cell arises from a backdrop of normal cells,
- $64\ 00:04:33.819 \longrightarrow 00:04:40.720$ doing normal cell things, the immune system has to find specific signals of damage or mutations that
- $65\ 00:04:40.720 \longrightarrow 00:04:43.007$ look abnormal in order to recognize cancer.
- $66~00:04:43.007 \dashrightarrow 00:04:46.233$ So you're telling me that normally it won't do that?
- 68 00:04:48.156 --> 00:04:54.451 Some tumors are recognized by the immune system and the immune system can actually get rid of them,
- $69\ 00:04:54.451 --> 00:05:02.615$ 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
- 70 00:05:02.615 --> 00:05:07.141 the immune system and turn them into tumors that the immune system can see and destroy?
- $71\ 00:05:07.141 \longrightarrow 00:05:10.750$ And so it seems to me that if you take that problem just at its face,
- $72\ 00:05:10.750 --> 00:05:13.264$ there are two ways of doing that.
- 73~00:05:13.264 --> 00:05:18.617 One is to make the tumor look more abnormal so that the immune system
- 74 00:05:18.617 --> 00:05:27.904 realizes, I need to attack it and get rid of it without actually revving up the immune system or getting rid of the
- $75\ 00:05:27.904$ --> 00:05:36.675 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.
- 76~00:05:36.675 --> 00:05:41.899 Yeah, that's right, and I think people are working at both sides of that problem.
- $77\ 00:05:41.899 --> 00:05:49.271$ We and others in the lab, are thinking of strategies both to make tumors put out signs for the immune system, saying,
- $78\ 00:05:49.271 \longrightarrow 00:05:55.995$ come get me and also looking for new ways to charge the immune system to be more aggressive against cancer.
- 79 00:05:55.995 --> 00:05:57.940 Tell us more about the first,
- $80\ 00:05:57.940 --> 00:06:04.721$ because I think that we've heard a little bit about checkpoint inhibitors,
- 81~00:06:04.721 --> 00:06:11.267 but we really haven't heard a lot about the work that's going on to have tumor cells put out those signs that

- 82 00:06:11.267 --> 00:06:22.262 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
- 83 00:06:22.262 --> 00:06:24.663 get rid of these cancer cells,
- $84\ 00:06:24.663 \longrightarrow 00:06:26.910$ because one of the problems,
- 85~00:06:26.910 --> 00:06:35.040 as you point out, of having a supercharged immune system is that it can then attack its own cells.
- 86 00:06:35.040 --> 00:06:37.966 Yeah, that's a great point and
- $87\ 00:06:37.966 \longrightarrow 00:06:42.720$ we've been thinking, and others as well,
- 88 00:06:42.720 --> 00:06:49.041 that it comes down to tricking the tumor cell into making inflammatory signals,
- 89 00:06:49.041 --> 00:06:56.002 tricking it into making kind of an antiviral response that recruits anti tumor immune cells into the micro environment,
- $90\ 00:06:56.002 \longrightarrow 00:06:57.336$ and I think
- 91 00:06:57.336 --> 00:07:06.963 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
- $92\ 00:07:06.963 \longrightarrow 00:07:10.675$ directly around the tumor.
- $93\ 00:07:10.675 \longrightarrow 00:07:15.610$ Tell us more about that work, is that actually something that's being done?
- 94 00:07:15.610 --> 00:07:19.267 Is it in clinical practice?
- 95 $00:07:19.267 \longrightarrow 00:07:20.778$ How do we do that?
- 96 00:07:20.778 --> 00:07:29.605 There are a number of clinical trials now using stimulators of viral pathways that look like DNA or RNA,
- $97\ 00:07:29.605$ --> 00:07:36.523 things that viruses make and that ourselves have dedicated sensors in order to detect.
- $98\ 00:07:36.523$ --> 00:07:42.485 and I think none of them has proven to be the Magic bullet for cancer yet.
- 99 00:07:42.485 --> 00:07:46.779 But there are still some technical hurdles to workout.
- 100 00:07:46.779 --> 00:07:49.764 And I think we're getting there though.
- $101\ 00:07:49.764 \longrightarrow 00:07:56.178$ Why has that not proven to be as successful as supercharging the immune system?
- $102\ 00:07:56.178 --> 00:08:03.264\ I$ think one of the challenges is that cancer in many cases can spread to many locations,

- $103\ 00:08:03.264 --> 00:08:09.158$ and when you think about triggering an inflammatory response in the tumor bed,
- 104 00:08:09.158 --> 00:08:12.439 you're really thinking about triggering it,
- $105\ 00:08:12.439 \longrightarrow 00:08:14.081$ not just at one site,
- 106 00:08:14.081 --> 00:08:16.394 but at many sites all at once,
- $107\ 00:08:16.394 \longrightarrow 00:08:18.930$ and so finding ways to send drugs
- 108 00:08:18.930 --> 00:08:26.410 to all of the different sites that cancer occupies in the body is one of the major challenges to getting this approach to work.
- $109\ 00:08:26.410 \longrightarrow 00:08:33.524$ The other approach then is the one that is the mainstay of immunotherapy,
- 110 00:08:33.524 --> 00:08:38.844 which is to quote supercharge the immune system to get rid of the blocks.
- $111\ 00:08:38.844 \longrightarrow 00:08:43.157\ I$ always think of it like Harry Potters invisibility cloak,
- $112\ 00:08:43.157 --> 00:08:48.403$ right. The tumor has kind of made itself invisible to the immune system,
- 113 00:08:48.403 --> 00:08:57.100 and it's getting rid of that that cloak and getting the immune system to recognize it and to go after it and two,
- $114\ 00:08:57.100 \longrightarrow 00:08:59.630$ to be quote supercharged now.
- 115 00:08:59.630 --> 00:09:09.755 You mentioned two molecules, in particular CTL A4 and PDL1, tell us a little bit about the differences between the two.
- $116\ 00:09:09.755 \dashrightarrow 00:09:14.227\ I$ mean we have drugs that will block either pathway.
- 117 00:09:14.227 --> 00:09:17.602 How do you figure out which one to use?
- 118 00:09:17.602 --> 00:09:20.556 Tell us more about that interplay.
- 119 00:09:20.556 --> 00:09:29.019 I think we still don't fully understand the mechanism of either drug and either pathway.
- 120 00:09:29.019 --> 00:09:32.062 And people have done a lot of good work,
- $121\ 00:09:32.062$ --> 00:09:36.102 in fact, the Nobel Prize was awarded a few years back for some of that work,
- $122\ 00:09:36.102 \longrightarrow 00:09:39.042$ but I wouldn't say that we completely understand which,
- $123\ 00:09:39.042 --> 00:09:41.508$ even sometimes which cells are being targeted,
- $124\ 00:09:41.508 --> 00:09:44.918$ but certainly which pathways within the cell are being activated.

 $125\ 00:09:44.918 \longrightarrow 00:09:47.961$ So a lot of how we figured this out has been empirically.

126 00:09:47.961 --> 00:09:52.369 We've done clinical trials with different drugs or different combinations of drugs,

 $127\ 00:09:52.369 \longrightarrow 00:09:55.044$ and we've seen what's been effective for patients,

 $128\ 00:09:55.044 \longrightarrow 00:09:59.085$ and the hope is going forward that as we learn more about the immune system,

 $129\ 00:09:59.085$ --> 00:10:04.150 and as we learn more about the tumor that we will be able to do better

 $130\ 00:10:04.150 \longrightarrow 00:10:09.876$ and even predict the next set of these drugs that could be usefully combined.

 $131\ 00:10:09.876 --> 00:10:14.153$ So tell us more about the differences between CTLA for an PDL1.

132 00:10:14.153 --> 00:10:24.486 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,

 $133\ 00:10:24.486 \longrightarrow 00:10:26.264$ and seeing that they work.

 $134\ 00:10:26.264 --> 00:10:29.620$ But we must know more about these actual molecules.

 $135\ 00{:}10{:}29.620 \dashrightarrow 00{:}10{:}33.971$ Yeah, they both play an inhibitory role in T cells.

136 00:10:33.971 --> 00:10:37.220 I think it's broadly thought

 $137\ 00:10:37.220$ --> 00:10:42.621 that one of them plays more of a role in T cells initially getting primed against the tumor,

 $138\ 00:10:42.621$ --> 00:10:52.032 but maybe plays more of a role in lymph nodes then generating the T cells that are capable of responding whereas the other one,

 $139\ 00:10:52.032$ --> 00:11:01.325 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.

 $140\ 00:11:01.325$ --> 00:11:08.470 And I'm going to steer clear of the term of exhaustion because there are a lot of debates about whether T cells

141 00:11:08.470 --> 00:11:10.476 are actually exhausted or not,

 $142\ 00:11:10.476$ --> 00:11:20.903 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

143 00:11:20.903 --> 00:11:23.557 of the things that PDL1 blockade does,

 $146\ 00:11:27.120 --> 00:11:31.986$ is to make the T cells that have become dysfunctional more functional.

 $147\ 00:11:31.986 \longrightarrow 00:11:35.620$ And so if these two pathways then are complementary,

148 00:11:35.620 --> 00:11:42.269 one being more so for priming T cells and one being more so for T cells that are already primed,

149 00:11:42.269 --> 00:11:53.511 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?

 $150~00{:}11{:}53.511 \dashrightarrow 00{:}11{:}56.664$ There has, and in Melanoma combining two drugs,

151 00:11:56.664 --> 00:11:58.309 one that targets CTL A4.

152 00:11:58.309 --> 00:12:07.804 and one that targets PDL1 seems to be better than using either drug alone and potentially better than using them both in sequence,

 $153\ 00:12:07.804 \dashrightarrow 00:12:17.014$ although the latter is a less clear conclusion.

 $154\ 00:12:17.014 --> 00:12:27.578$ 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.

 $155\ 00:12:27.578 --> 00:12:39.287$ 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

 $156\ 00:12:39.287 --> 00:12:45.355$ can just be removed and surgically cut out in the early stages and really beyond Melanoma,

157 00:12:45.355 --> 00:12:53.691 it spread throughout many many solid tumor types and it's being tried in almost any tumor type you can think of.

 $158\ 00:12:53.691 --> 00:13:00.360$ And so two questions. First question is one of the things you mentioned earlier as being one of the

 $159\ 00:13:00.360 --> 00:13:08.214$ downfalls of some therapies is that it can't always get to all of the cells where the tumors may be hiding.

160 00:13:08.214 --> 00:13:16.735 Does immunotherapy have that problem in terms of getting to the T cells and activating them or supercharging them?

 $161\ 00{:}13{:}16.735 \dashrightarrow 00{:}13{:}21.847$ Or is that concept, this may not work if there's a tumor,

162 00:13:21.847 --> 00:13:23.774 for example in the brain?

 $163\ 00{:}13{:}23.774 \longrightarrow 00{:}13{:}27.850$ Because this drug can't cross the blood brain barrier?

164 00:13:27.850 --> 00:13:31.500 Or does it affect T cells wherever they are?

 $165\ 00:13:31.500 --> 00:13:38.470$ We know that we can get effects certainly in the brain.

 $166\ 00:13:38.470 \longrightarrow 00:13:51.299$ 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

167 00:13:51.299 --> 00:13:53.327 I guess what I don't know for sure,

168 00:13:53.327 --> 00:13:58.621 it's hard to say is whether there is a problem activating immune cells somewhere in the body.

169 00:13:58.621 --> 00:14:07.352 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.

170 00:14:07.352 --> 00:14:14.505 We're going to learn a lot more about Melanoma immunotherapy right after we take a short break for a medical minute.

 $171\ 00:14:14.505 --> 00:14:22.730$ Please stay tuned to learn more about this research with my guest doctor Jeffrey Ishizuka. Support for Yale Cancer Answers comes from AstraZeneca.

172 00:14:22.730 --> 00:14:28.499 Providing important treatment options for patients with different types of lung,

173 00:14:28.499 --> 00:14:31.631 bladder, ovarian, breast, and blood cancers.

 $174\ 00:14:31.631 --> 00:14:35.570$ More information at astrazeneca-us.com.

175 00:14:35.570 --> 00:14:38.466 This is a medical minute about breast cancer,

 $176\ 00:14:38.466$ --> 00:14:41.866 the most common cancer in women. In Connecticut alone,

 $177\ 00:14:41.866 --> 00:14:46.462$ approximately 3000 women will be diagnosed with breast cancer this year,

 $178\ 00:14:46.462 --> 00:14:48.541$ but thanks to earlier detection,

179 00:14:48.541 --> 00:14:51.312 noninvasive treatments, an novel therapies,

 $180\ 00:14:51.312 --> 00:14:56.159$ there are more options for patients to fight breast cancer than ever before.

 $181\ 00:14:56.159$ --> 00:15:04.408 Women should schedule a baseline mammogram beginning at age 40 or earlier if they have risk factors associated with breast cancer.

 $182\ 00:15:04.408 --> 00:15:10.580$ Digital breast tomosynthesis or 3D mammography is transforming breast screening by significantly

 $183\ 00:15:10.580 --> 00:15:17.620$ reducing unnecessary procedures while picking up more cancers and eliminating some of the fear and anxiety

184 00:15:17.620 --> 00:15:22.706 many women experience. More information is available at yalecancercenter.org.

185 00:15:22.706 --> 00:15:26.840 You're listening to Connecticut public radio.

 $186\ 00:15:26.840 --> 00:15:29.259$ Welcome back to Yale Cancer Answers.

187~00:15:29.259 --> 00:15:35.341 This is doctor Anees Chagpar andnI'm joined tonight by my guest doctor Jeffrey Ishizuka.

 $188\ 00:15:35.341$ --> 00:15:41.226 We're talking about Melanoma research and in particular we're talking about immunotherapy.

 $189\ 00:15:41.226 --> 00:15:47.374$ Jeff, right before the break we were talking a little bit about immunotherapy in terms of,

 $190\ 00:15:47.374$ --> 00:15:51.754 really getting the immune system to attack cancer cells,

191 $00:15:51.754 \longrightarrow 00:15:55.024$ which it may not recognize because as you put it,

 $192\ 00{:}15{:}55.024 {\:{\mbox{--}}}{>}\ 00{:}15{:}58.360$ these cancer cells come from normal cells and that

193 00:15:58.360 --> 00:16:07.715 may not be as foreign looking to the immune system to really trigger it and we talked a little bit about two separate pathways,

 $194~00{:}16{:}07.715 \dashrightarrow 00{:}16{:}11.692$ CTL A4 and PDL1 and the fact that we now have drugs,

195 00:16:11.692 --> 00:16:20.974 this explosion of drugs in immunotherapy targeting these two pathways and how this really has become the mainstay of therapy,

196 00:16:20.974 --> 00:16:23.921 particularly for cancers like Melanoma.

 $197~00{:}16{:}23.921 \dashrightarrow 00{:}16{:}27.971$ I had a few questions to kind of follow up on that.

 $198\ 00{:}16{:}27.971 \dashrightarrow 00{:}16{:}32.494$ The first is, tell us a little bit about the side effects.

 $199\ 00:16:32.494 \longrightarrow 00:16:35.000$ We think about

200 00:16:35.000 --> 00:16:39.551 chemotherapy, and you know, traditionally,

 $201\ 00:16:39.551 --> 00:16:47.469$ chemotherapy was the rapy that kills off cancer cells and was really thought to be the rapy that switches off $202\ 00:16:47.469$ --> 00:16:55.184 rapidly dividing cells and so people ended up losing hair and maybe getting sick because it effects your GI lining,

 $203\ 00:16:55.184 \longrightarrow 00:16:57.711$ which are rapidly turning over cells.

 $204\ 00:16:57.711 \longrightarrow 00:17:01.171$ Do you get the same kind of thing in immunotherapy,

 $205\ 00{:}17{:}01.171 \dashrightarrow 00{:}17{:}05.560$ or are there other side effects that are the results of

 $206\ 00:17:05.560 --> 00:17:11.880$ kind of supercharging this immune system and getting the immune system to attack healthy cells?

 $207\ 00:17:11.880 \longrightarrow 00:17:13.540$ So I think that's it exactly.

208 00:17:13.540 --> 00:17:20.130 Many of the side effects that you get from immunotherapy are actually side effects of supercharging the immune system,

 $209\ 00:17:20.130 --> 00:17:24.227$ so the immune system can accidentally attack different areas of the body.

 $210\ 00{:}17{:}24.227 \dashrightarrow 00{:}17{:}27.383$ Some of the things we see are inflammation in the lungs,

 $211\ 00:17:27.383 --> 00:17:31.536$ inflammation in the GI system we see inflammation of the endocrine system,

 $212\ 00{:}17{:}31.536 {\:{\mbox{--}}}{>}\ 00{:}17{:}34.471$ and when we first started seeing these side effects,

 $213\ 00:17:34.471 \longrightarrow 00:17:37.183$ there wasn't a good sense of how you treat them,

 $214\ 00{:}17{:}37.183 \dashrightarrow 00{:}17{:}39.730$ how you manage them, or even how you monitor.

 $215\ 00:17:39.730 \longrightarrow 00:17:41.890$ We didn't really know what to look for.

216 00:17:41.890 --> 00:17:45.832 But I will say that as experience with these agents has progressed,

 $217\ 00{:}17{:}45.832 \dashrightarrow 00{:}17{:}49.715$ we've gotten better at detecting these side effects as they occur,

 $218\ 00:17:49.715$ --> 00:17:56.324 and managing them, usually using immunosuppressives and one of the questions that comes up when you start saying,

 $219\ 00:17:56.324 \longrightarrow 00:18:02.469$ well, you're using drugs to charge the immune system and at the same time to shut down the immune system,

 $220\ 00:18:02.469 \longrightarrow 00:18:05.772$ is that going to be is going to be bad for the patients.

221 00:18:05.772 --> 00:18:11.221 Are they going to have that outcomes and the data isn't really completely mature on this yet,

222 00:18:11.221 --> 00:18:14.119 but it certainly appears from the early data that

223 00:18:14.119 --> 00:18:22.204 you can safely give these immunosuppressives and that you don't at least don't clearly make their responses against the cancer

224 00:18:22.204 --> 00:18:26.121 worse.

225 00:18:26.121 --> 00:18:32.183 That's really interesting. Why would that be the case? I can imagine that when we think about people who are immunosuppressed,

226 00:18:32.183 --> 00:18:37.994 people who for example have HIV or other things that turn off their immune system,

227 00:18:37.994 --> 00:18:40.773 they are more at risk of developing cancer,

 $228\ 00:18:40.773$ --> 00:18:45.321 and I guess for the same reason that you talked about before the break.

229 00:18:45.321 --> 00:18:47.263 which is your immune system,

230 00:18:47.263 --> 00:18:55.902 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,

231 00:18:55.902 --> 00:19:01.900 and so if you are immuno compromised you're at increased risk of getting cancer,

232 00:19:01.900 --> 00:19:04.199 and that's the whole point of

233 $00:19:04.199 \longrightarrow 00:19:10.650$ supercharging the immune system to get rid of these cancers.

 $234\ 00:19:10.650 --> 00:19:21.922$ Why is it that giving people an immunosuppresant at the same time as an immuno supercharger doesn't seem to affect the cancer in a bad way?

235 00:19:21.922 --> 00:19:25.333 A couple of potential thoughts here.

 $236\ 00:19:25.333 \longrightarrow 00:19:32.230$ The first one is that I want to be careful we don't know for sure that it doesn't affect the

237 00:19:32.230 --> 00:19:34.575 response to therapy in a negative way.

 $238\ 00:19:34.575 \longrightarrow 00:19:37.099$ I think what we can say is that

 $239\ 00:19:37.099 --> 00:19:44.730$ at first blush, patients who needed immunosuppressives because they had these bad immune effects and got them didn't do obviously worse,

 $240\ 00:19:44.730 \longrightarrow 00:19:46.394$ at least in the early studies

241 00:19:46.394 --> 00:19:55.260 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

 $242\ 00:19:55.260 \longrightarrow 00:19:58.968$ actually were having the strongest immune responses to begin with,

243 00:19:58.968 --> 00:20:08.329 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.

 $244\ 00{:}20{:}08.329 \dashrightarrow 00{:}20{:}14.859$ And I think that's probably the main thing that I would think about for that issue.

 $245\ 00:20:14.859 --> 00:20:20.846$ The other question that I have is, these autoimmune side effects,

246 00:20:20.846 --> 00:20:26.355 the side effects of people's immune system now attacking their own normal cells,

 $247\ 00:20:26.355 \longrightarrow 00:20:28.532$ are those permanent? Are

248 00:20:28.532 --> 00:20:37.578 they forever or are they short lived? I mean when you get chemotherapy and you lose your hair,

 $249\ 00:20:37.578 \longrightarrow 00:20:39.319$ your hair will grow back.

 $250\ 00:20:39.319 --> 00:20:44.597$ Is it the same with immunotherapy that this is a short term thing?

 $251\ 00:20:44.597 \longrightarrow 00:20:47.416$ Or when your immune system attacks your lungs,

252 00:20:47.416 --> 00:20:50.776 now you've got pulmonary fibrosis forever?

 $253\ 00:20:50.776$ --> $00:20:55.694\ I$ think it depends on the type of immune side effect that we're talking about.

254 00:20:55.694 --> 00:20:57.013 I think many of them,

 $255\ 00:20:57.013 \longrightarrow 00:20:59.833$ if they're controlled with immunosuppressives,

 $256\ 00:20:59.833 \longrightarrow 00:21:04.332$ and if you take the patient off of the immunotherapy, will actually go away.

 $257\ 00:21:04.332 \longrightarrow 00:21:06.371$ So we see this in a lot of cases,

 $258\ 00{:}21{:}06.371 \dashrightarrow 00{:}21{:}09.730$ inflammation in the colon, or inflammation in the lungs.

 $259\ 00:21:09.730 \longrightarrow 00:21:16.951$ I think the case in which this isn't necessarily true is when the immune system attacks the cell type

260 00:21:16.951 --> 00:21:26.278 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

 $261\ 00{:}21{:}26.278 \dashrightarrow 00{:}21{:}30.440$ is gone, and after that there's really no bringing it back.

 $262\ 00:21:30.440 \longrightarrow 00:21:37.403$ So in most cases we actually have been able to give hormone replacement.

 $263\ 00:21:37.403 \longrightarrow 00:21:40.398$ It's extremely bad if it's not detected,

 $264\ 00:21:40.398 \longrightarrow 00:21:45.001$ but in a lot of cases it can be solved by giving a pill a day.

265 00:21:45.001 --> 00:21:47.413 When you talk about hormones,

266 00:21:47.413 --> 00:21:54.430 are you talking about thyroid are you talking about ovaries, what hormones are we talking about?

267 00:21:54.430 --> 00:21:57.801 Yeah, so thyroid is one that you certainly see,

 $268\ 00:21:57.801 \longrightarrow 00:22:05.179$ but you see actually a number of other hormones that are produced in the brain that can also be altered,

 $269\ 00:22:05.179 \longrightarrow 00:22:07.356$ and these can be be more rare,

270 00:22:07.356 --> 00:22:10.449 but can be pretty dramatic if you see them.

 $271\ 00:22:10.449 \longrightarrow 00:22:14.289$ So given the side effects of immunotherapy,

 $272\ 00:22:14.289 --> 00:22:17.953$ is immunotherapy really better than classic chemotherapy?

 $273\ 00:22:17.953 --> 00:22:24.209$ You had mentioned that immunotherapy has now become standard of care for Melanoma.

 $274\ 00:22:24.209 \longrightarrow 00:22:26.925$ Is it better than what we used to do?

276 00:22:28.758 --> 00:22:31.474 We used to give chemotherapy for Melanoma,

277 00:22:31.474 --> 00:22:32.991 right?

 $278\ 00:22:32.991$ --> 00:22:36.846 And Melanoma is not particularly responsive to chemotherapy,

 $279\ 00:22:36.846 --> 00:22:41.268$ and I think what excited everyone in the field and it's given us all

 $280\ 00:22:41.268 --> 00:22:44.680$ a lot of excitement and a lot of hope is not even that

 $281\ 00:22:44.680 \longrightarrow 00:22:48.277$ everyone responds to these immunotherapy's because they don't,

 $282\ 00:22:48.277 --> 00:22:52.444$ not enough patients do, and that's something we don't really understand.

283 00:22:52.444 --> 00:22:54.842 We're trying to understand it in the lab,

284 00:22:54.842 --> 00:22:59.238 but it's that some of the patients who respond seem to just keep responding,

 $285\ 00:22:59.238 \longrightarrow 00:23:07.002$ 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,

 $286\ 00{:}23{:}07.002 \dashrightarrow 00{:}23{:}10.371$ the immunotherapy drugs, and that the cancer won't return.

 $287\ 00:23:10.371$ --> 00:23:15.210 And this is true even in some cases for very aggressive disease.

 $288\ 00:23:15.210 \longrightarrow 00:23:19.686$ And so seeing those effects are the ones that have really made everybody excited.

289 00:23:19.686 --> 00:23:26.730 And you see that in clinical trials when we study how patients survive on different drugs and

 $290\ 00:23:26.730 \longrightarrow 00:23:30.730$ it was no contest between the immunotherapy's and chemotherapy.

291 00:23:30.730 --> 00:23:44.059 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

292 00:23:44.059 --> 00:23:48.154 eat, what receptors cancer has,

293 00:23:48.154 --> 00:23:51.446 what genes are turned on and turned off,

294~00:23:51.446 --> 00:23:54.900 and then we target our therapy accordingly.

 $295\ 00:23:54.900$ --> 00:24:04.340 Talk about immunotherapy. It seems to me like we're talking about a blanket turning on supercharging the immune system,

 $296\ 00:24:04.340 \longrightarrow 00:24:09.962$ is that right, or are there ways where we're actually tailoring this therapy?

297 00:24:09.962 --> 00:24:20.484 Are we looking at who those people are that are super responsive to immunotherapy versus the people who are not super responsive to immunotherapy?

 $298\ 00:24:20.484 \longrightarrow 00:24:25.170$ And which immunotherapy might work better in particular patients?

 $299~00{:}24{:}25.170 \dashrightarrow 00{:}24{:}28.638$ Yeah, so this question is near and dear to my heart.

 $300\ 00:24:28.638 --> 00:24:39.308$ 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

 $301\ 00:24:39.308 \longrightarrow 00:24:43.237$ we talked about PDL1 and PD1 is one of these key pathways,

302 00:24:43.237 --> 00:24:51.484 so if you have PDL1 expressed in the tumor microenvironment either by immune cells in the micro environment or by the tumor,

 $303\ 00:24:51.484 \longrightarrow 00:24:57.809$ we know that you are more likely to have a response to targeting the PD1 PDL1 axis.

304 00:24:57.809 --> 00:25:07.530 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

 $305\ 00:25:07.530 \longrightarrow 00:25:10.712$ in their tumor who won't respond well to these drugs.

 $306\ 00:25:10.712 --> 00:25:18.018$ And conversely, there are a lot of patients who won't have PDL1 expression in the tumor who will still respond to these drugs.

 $307\ 00:25:18.018 --> 00:25:20.257$ So what's the point of the biomarker then?

 $308\ 00:25:20.257 --> 00:25:28.799$ 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

 $309\ 00:25:28.799 --> 00:25:32.184$ a signal of the drug working in a patient population and unless,

 $310\ 00:25:32.184$ --> 00:25:37.234 you used a biomarker, and also it's a stand in because we haven't done a good enough job yet of

 $311\ 00:25:37.234 \longrightarrow 00:25:40.563$ finding better ones.

 $312\ 00:25:40.563 \longrightarrow 00:25:44.446$ So we have this biomarker that if you have it,

 $313\ 00:25:44.446 \longrightarrow 00:25:49.421$ you won't necessarily respond to the immunotherapy, if you don't have it,

314 00:25:49.421 --> 00:25:52.009 you may still respond to the therapy,

 $315\ 00:25:52.009 --> 00:25:57.257$ so either way you're likely going to get immunotherapy if you have Melanoma,

 $316~00{:}25{:}57.257 \dashrightarrow 00{:}26{:}01.430$ regardless of whether you have the biomarker or not.

 $317\ 00:26:01.430 \longrightarrow 00:26:06.644$ That's true, and that's where I think we have the potential to do much better,

 $318\ 00:26:06.644 \longrightarrow 00:26:10.737$ particularly as we talked about these two pathways,

319 00:26:10.737 --> 00:26:19.978 there are a lot of other immuno regulatory pathways that can activate immune cells or can activate the tumor to recruit immune cells.

 $320\ 00:26:19.978 \longrightarrow 00:26:23.740$ And we're still at the beginning of understanding these.

321 00:26:23.740 --> 00:26:31.859 But as these drugs come out and as they are available we have the potential to start thinking about OK for a given patient.

322 00:26:31.859 --> 00:26:37.201 How can we assess that patients immune system and how can we understand the tumor,

323 00:26:37.201 --> 00:26:45.880 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.

324 00:26:45.880 --> 00:26:48.942 That sounds really interesting,

325 00:26:48.942 --> 00:26:59.007 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

 $326\ 00{:}26{:}59.007 \dashrightarrow 00{:}27{:}02.883$ better. What targeted pathways are turned on versus turned off.

327 00:27:02.883 --> 00:27:09.695 Should you be using, you know an anti HER-2 agent in somebody who's got a HER-2-positive breast cancer?

 $328\ 00{:}27{:}09.695 \dashrightarrow 00{:}27{:}12.759$ Or should you be targeting KRAS in lung cancer?

 $329\ 00{:}27{:}12.759 \dashrightarrow 00{:}27{:}16.509$ Sounds like you're moving in the same direction in Melanoma.

330 00:27:16.509 --> 00:27:19.384 But looking at it from an immune perspective,

 $331\ 00:27:19.384 \longrightarrow 00:27:23.884$ and I should say this is mostly on the research side,

 $332\ 00:27:23.884 \longrightarrow 00:27:29.884$ right now we're trying to understand the flavors of inflammation in the tumor microenvironment.

 $333\ 00:27:29.884 \longrightarrow 00:27:35.009$ The composition of the immune cells that are there and why they're there,

 $334\ 00:27:35.009 --> 00:27:44.134$ 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,

 $335\ 00:27:44.134 \longrightarrow 00:27:46.759$ if we study them in a dish and treat them

 $336\ 00:27:46.759 --> 00:27:52.940$ with different immunotherapy drugs, can we see patterns of response from some patients but not from others?

 $337\ 00:27:52.940 --> 00:27:55.515$ Those are things that we're working on here,

 $338\ 00:27:55.515 \longrightarrow 00:28:01.237$ and others are working on as well that we think could lead to the development of better biomarkers.

 $339\ 00:28:01.237 \longrightarrow 00:28:03.239$ That's one kind of major approach.

340 00:28:03.239 --> 00:28:09.248 Another one is focusing on the technologies that have emerged to sequence patient genomes.

 $341\ 00:28:09.248 --> 00:28:11.479$ The immune cells from patient genomes.

 $342\ 00{:}28{:}11.479 \dashrightarrow 00{:}28{:}15.141$ We do technologies now to look at individual cells in sequence.

343 00:28:15.141 --> 00:28:17.460 Everything that that cell is expressing.

344 00:28:17.460 --> 00:28:24.708 Basically everything it's doing and we can do that for a bunch of cells in the micro environment all at once,

 $345\ 00:28:24.708$ --> 00:28:33.669 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.

 $346\ 00:28:33.669 --> 00:28:40.851$ We may find particular features of the immune system that interact with the tumor as well that predict that,

347 00:28:40.851 --> 00:28:47.045 and so I think that in the next 5 or 10 years we're likely to see progress in this direction.

 $348\ 00:28:47.045 \longrightarrow 00:28:50.009$ Whether that will translate affectively into

 $349\ 00:28:50.009 \longrightarrow 00:28:53.933$ guiding precise therapy choice for a patients

350 00:28:53.933 --> 00:28:59.750 Melanoma, I'm not sure.

 $351\ 00:28:59.750 \longrightarrow 00:29:01.787$ When you talk about,

352 00:29:01.787 --> 00:29:09.392 essentially taking tumors and looking at the micro environment and seeing the composition of these cancer cells,

 $353\ 00:29:09.392 \longrightarrow 00:29:13.125$ and what kinds of immune therapy they may benefit from,

 $354\ 00:29:13.125 --> 00:29:16.656$ you can also look at the immune system and see,

 $355\ 00:29:16.656$ --> 00:29:23.922 maybe my immune system is different from your immune system in terms of attacking a particular cell.

 $356\ 00:29:23.922 \longrightarrow 00:29:26.366$ Is that on the right track?

357 00:29:26.366 --> 00:29:28.606 It's exactly on the right track,

 $358\ 00:29:28.606 \longrightarrow 00:29:36.617$ and you know, even taking a step back when we first started to see that these therapies could work for patients,

359 00:29:36.617 --> 00:29:38.384 people started to ask,

 $360\ 00:29:38.384 \longrightarrow 00:29:41.982$ why do they work for some patients but not for others?

 $361\ 00:29:41.982 --> 00:29:51.471$ 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

362 00:29:51.471 --> 00:29:54.480 even prior to immunotherapy and others don't.

363 00:29:54.480 --> 00:29:56.509 And just unpacking that basic

364 00:29:56.509 --> 00:30:00.107 observation is something we're still doing,

 $365\ 00:30:00.107 --> 00:30:09.059$ but as I was mentioning, as we start to understand it as we start to understand the chemical signals that the tumor in the immune system makes.

 $366\ 00:30:09.059 \longrightarrow 00:30:15.050$ It's giving us a lot of inputs to try to determine which drugs could be affective in each case,

 $367\ 00{:}30{:}15.050 \dashrightarrow 00{:}30{:}18.796$ and what the basic flavors of immune micro environment are.

 $368\ 00:30:18.796 --> 00:30:25.098$ Doctor Jeffrey Ishizuka is an Assistant Professor of Medical Oncology at the Yale School of Medicine.

369 00:30:25.098 --> 00:30:35.021 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.

 $370\ 00:30:35.021$ --> 00:30:39.890 We hope you'll join us next week to learn more about the fight against cancer

371 00:30:39.890 --> 00:30:43.248 here on Connecticut Public Radio.