Conquering Cancer from Within. Immunotherapy, the new Hope.

Immunotherapy is a type of cancer treatment that helps your immune system fight cancer. Several types of immunotherapy are used to treat cancer. These treatments either re-engineer the immune cells or empower them to launch an attack on the cancer directly.

Immunotherapy has led to remarkable results for some cancers, eradicating difficult-to-treat tumors and, in some cases, causing complete remission of disease. We are talking to Dr. Lawrence Fong who leads the Cancer Immunotherapy Program at UCSF Helen Diller Family Comprehensive Cancer Center about the latest in the field in terms of research, clinical trials and treatments currently available.

Full Transcript:

Priya Menon: Good afternoon and welcome to another episode of Cure Talks. I'm Priya Menon, your host and today the topic of our discussion is Cancer Immunotherapy. We are joined by Dr Lawrence Fong from UCSF Helen Diller Family Comprehensive Cancer Center. On the patient panel, to discuss the patient perspective, we have patient advocates, Mike Scott, David Stanley, Joel Nowak and Amy Marash. Dr Fong, great to have you with us and welcome to Cure Talks.

Dr Lawrence Fong: Well, thank you for having me.

Priya: Dr Fong, you were part of the team that brought the first immunotherapy drugs from the labs to clinic. It would be great if you could talk a little bit about this fascination with the immune system and your journey in being able to treat cancer with your own immune system.

Dr Lawrence Fong: Well, my interest in focusing on cancers is a bit personal. My father died of cancer while I was in college. So I decided to go into medical school hoping to work on new treatments for this disease. And while I was in medical school, I actually became intrigued by the complexity and power of the immune system while taking the introductory immunology course during my first year in medical school. If the immune system could target certain types of infections with fine specificity, why couldn't we use it to treat cancer? And at that time I was in med school, there were some immunotherapies just starting to make their way into the clinic, these cytokine therapies and cancer vaccines. And so, I decided for my research training in fellowship to really dive into this.

And so I decided to work on immunotherapy for solid cancers including prostate cancer. I recall one of my

professors at the time telling me that this approach would never work. Nevertheless, I worked with groups at Stanford, including Doctor Ed Engleman on a dendritic cell vaccine for prostate cancer. And this ultimately became an FDA approved therapy called Sipuleucel-T or Provenge. When I moved to UCSF, we continued with our interest in immunotherapy and I had a chance to work on the first human trial with another immunotherapy. This was an anti-CTLA 4 antibody, which is now called Ipilimumab and is also FDA approved. And since that time, there have been other therapies really making their way into the clinic, especially these anti-PD-1 antibodies that we've worked on. And it's been a very wild ride ever since.

Priya: It has probably taken decades of basic research to understand the fundamentals of our immune system, and then probably overlay on them the fundamentals of cancer and then further overlay how the two of these things work together and then try to come up with a solution. It's truly fascinating. Do you think this is the Penicillin moment for cancer?

Dr Lawrence Fong: Ah, wow. Yes and no. Yes in that, our approach to treating cancer has forever changed, not unlike when penicillin came out. Just as patients with bacterial infections now receive antibiotics, I think the majority of cancer patients in the future will receive immunotherapy. In fact, we now teach our medical students about cancer immunotherapy in their introductory class if they actually started out in medical school. So it's really changed our way of thinking. Unfortunately, the challenge is that our current immunotherapies do not work as well as a penicillin. Only 10 to 30% of our cancer patients benefit with our current immunotherapies when they work. For those patients they may have very durable responses including some folks being cured. Our challenge is now to get immunotherapies to work in more people.

Priya: Dr Fong, I'm going to ask quite a broader question here. So could you please talk about some of the most effective cancer immunotherapies that we know today?

Dr Lawrence Fong: Well, there are three areas where immunotherapy has had great success at this point and those are immune checkpoint inhibition, bi-specific antibodies and the third are CAR-T cell therapies. With immune checkpoint inhibitors, these are the antibodies that target CTLA-4 or PD-1 or its receptor PD-L1. These different molecules are essentially brakes on the immune system. And by giving these antibodies, we're blocking those brakes so that we can turn or revive the immune system to target the cancer. These antibodies can lead to responses in a broad range of cancer and the list of approvals where we can administer these drugs is getting longer by the day it seems. We've also found that combining these checkpoint inhibitors such as anti-PD-1 and anti-CTLA-4, we can actually see better response rates in certain diseases such as melanoma and kidney cancer and for some lung cancers.

With regards to that second area bi-specific antibodies, these are drugs where one end of the drug targets the cancer cell and the other end targets the immune system. By pulling these immune cells into the tumors we're banking on these immune cells, killing the tumors and in fact, we've got a drug already FDA approved for B-cell malignancies that does this. The third area are these CAR-T cells or what are called Chimeric Antigen Receptor T- cells. With this treatment, we take immune cells out of a patient. We actually engineer those cells so that they have a receptor that targets the cancer cell. And then we give those cells back to the patient. So these immune cells are now hardwired to recognize the cancer and we now have multiple CAR-T cells approved, better targeting B cell leukemias and lymphomas.

Priya: Dr Fong, you already just mentioned CAR-T cells, I'm going to take an audience question on this. The person listening wants to know can T-cell therapies be used against common solid tumors?

Dr Lawrence Fong: Well, right now that's a very active area of investigation. As I mentioned, the CAR-T cells that we currently have approved, target B cell malignancy. So these are leukemias and lymphomas. With regards to solid tumors, that's proved to be a bigger challenge. And one of the challenges is actually finding a good target on a solid tumor. And, there are multiple groups that are working on this and groups are also looking at ways where we don't rely on just one protein, but we might rely on integrating a recognition of multiple proteins to target and kill the tumor cell. The other element is with regards to solid tumors, the tumors themselves are very inhospitable for immune cells. And so we're also thinking about ways to make

these CAR-T cells resistant to those suppressive mechanisms, so they actually work better there. And so this would be an area that I really recommend staying tuned as these new cell therapies come into the clinic.

Priya: Absolutely. So we have another question on the same lines of CAR-T and engineering of their genes for these re-engineered T-cells. So can Dr Fong talk about CRISPR and how it can help cancer immunotherapy?

Dr Lawrence Fong: Yeah. So CRISPR is a new way to edit genes in cells and CRISPR therapies are being developed to target specific cell types within the body. CRISPR has also been used to engineer cells outside the body, in this context taking out, for instance T-cells and editing in a receptor that's targeting the tumors. And so this is a new technology that's just made its way into the clinic and over time I think as we learn more how to use CRISPR, we will more than likely see this being used in more and more clinical trials. And it should make a engineering of the cells easier than the methods that we use today.

Priya: Thank you Dr Fong. Going back to have initial trail of questions that we were talking about checkpoint inhibitors and CAR-T cells. So as you said, Dr, immunotherapy does not work for all tumors. It follows that other drugs can combine with immunotherapies. So it would be great if you could talk a little bit about the impact of immunotherapies on the scope of combination therapies?

Dr Lawrence Fong: Yeah. So, I mentioned briefly that, we're now combining anti-CTLA-4 and anti-PD-1 for some cancers. Really an area of active research is if identifying other immunotherapies that we can combine together, including combining with these existing antibodies that we have. But importantly, we've also found that we can combine immunotherapies with our conventional cancer treatments such as chemotherapies and targeted therapies. As it turns out, these cancer therapies that we've used for years can also affect the immune system. And so now we actually use a combination of an anti-PD-1 antibody with chemotherapy for the first line of treatment in lung cancer. And we're also now able to use that in some breast cancers. With regards to targeted therapies, we have these drugs that target blood vessels, what we call tyrosine kinase inhibitors or TKIs. What we found is you can actually use these drugs to combine with anti-PD-1 antibodies. And this is now an FDA approved frontline therapy for kidney cancer. And so as we learn how other cancer treatments modify the immune system, we're looking forward to more and more combinations with immunotherapies in the future.

Priya: Thank you. Dr Fong. So what do you see, I know you're talking about combination therapies and targeted therapies, so what do you see as the next major milestone in cancer immunotherapy over the next five years. And we'd also like to know about the programs that UCSF Helen Diller Center that a patient should keep track of?

Dr Lawrence Fong: Yeah. So, over the next five years, first, I hope that we'll see new drugs targeting other immune pathways gaining traction. Right now a lot of interest is around the immune checkpoints, but there clearly are other pathways that are also incredibly important. And as we get more of those drugs available, this will add to our treatment toolkit going forward. Second, I think our understanding and our ability to identify who can respond to these immunotherapies will improve over the next five years. And so, this is important for us to not only give our existing immunotherapies to patients who we believe to respond, but it would also be important for us to be able to select and identify patients who might need combination therapies or other treatments added to their immunotherapy.

Ultimately, we'd love to be able to tailor immunotherapy to each patient, to this idea of precision cancer treatment. And I think that would be possible in immunotherapy as well. Finally, I think over that timeframe we'll see CAR-T cells and bi-specific antibodies that will work on more cancers. Right now, we only have those treatments approved for B-cell malignancies as we talked about. But I think, over the next five years, we'll see that broaden out to other diseases. In terms of your question about the cancer immunotherapy program at UCSF, this is a program that is focused on bringing new immunotherapies into the clinic. Historically, cancer centers and programs had focused programs on where the cancer arises from.

So for instance, from the lung or from the breast or from the prostate. Our program actually is focused on the treatment modality which is using the immune system to treat cancer because there are specific considerations and how we can administer these safely as well as how we can get them to work better. And so within this program we have clinical trials that span different diseases. This includes new checkpoint inhibitors, vaccines, bi-specifics and cell therapies. Our mission is to learn as much as we can from each person that we care for. And so to realize that vision, we have clinical and laboratory researchers integrated into this immunotherapy program. What that allows us to do is to perform cutting edge research on samples from our patients. And really to tease out what these immunotherapies are doing in, in people with cancer.

I'm often asked by people I'm caring for, how their immune system is responding to the treatment. We hope with further research that we'll be able to answer these questions in the future and that these types of discoveries will help guide new immunotherapies and new immunotherapy combinations. And so, it really is a program that has multiple clinical trials going on now, and we have over 20 clinical trials. But we also have a pipeline of even more trials that will be activating. But importantly we hope to not only to be administering these treatments, but again, really advancing the field with new discoveries.

Priya: That sounds really interesting, Dr Fong. I'm going to actually stop my questions now and let the panel take over for a while. Before that, I want to just take one question from the audience. This person wants to know we have been reading about cancer vaccines. In fact, Stanford has a human trial on, for vaccines. Dr Fong, where do we stand with respect to vaccines for cancer?

Dr Lawrence Fong: So right now, the only FDA approved cancer vaccine for treating patients with cancer is Sipuleucel-T or Provenge. And that's FDA approved for men with advanced metastatic prostate cancer. There are studies now focused on a whole host of different vaccines. That vaccine that I described targets a protein that's expressed on prostate cancer, and so it's can be administered to a broad range of prostate cancer patients. But one area of research now that's quite active and we also have multiple clinical trials studying this at UCSF is to use customized vaccines. And so in this approach, what we do is using a biopsy from a patient and that could either be one that was done in the past or one that we do for the clinical trial.

We actually sequence that individual's cancer to understand what types of mutations are present within that cancer. And because these mutations only arise in the cancer, we think that these would actually make great targets for a vaccine. And so with this sequence information, the companies that we're working with on these vaccines, basically create a specific vaccine for that specific individual. So it's customized. And so that vaccine is given to an individual and it's usually given in combination with a checkpoint inhibitor. And so right now we have a couple of those clinical trials going on at UCSF. I think this is an area of very active investigation and I would also recommend a staying tuned as we get and more experience with this approach.

Priya: Okay. So, with that I'm going to hand it over to David. David Stanley is a writer, teacher, actor and orator. His book on melanoma, titled Melanoma: It started with a Freckle, is available on Amazon. David, over to you.

David Stanley: Thank you Priya. Dr Fong, a pleasure. Thanks for being with us today. I appreciate it. I have a couple of questions for you. Priya, is this the way we are going to do this, I'll ask like my two or three questions and we'll move on to the next guest?

Priya: Yes, yes.

David: In the melanoma community, one of the big issues that a lot of the patients are having with the checkpoint inhibitors like Keytruda and Opdivo are the side effects. And some of them are just so devastating that even though the patients are getting good results from those checkpoint inhibitors, they have to stop treatment. Looking forward, what kinds of things are you thinking about in your lab to help ameliorate some of those horrible side effects with the checkpoint inhibitors kick off?

Dr Lawrence Fong: Yeah, this is a terrific question. This is one of the risks when we turn on the immune system to fight the cancer, we also turn on the immune system, that might lead to the immune system attacking some of these other tissues. And within our research program here, we actually are, are studying this, whereby, we're taking blood samples from patients starting with these checkpoint inhibitors and if they were to develop the toxicities, we'd again get blood samples from them. But also if there is an area that's being involved with this side effect, we actually take a biopsy of that. And in doing so, what we can do is finally dissect out what the immune system is actually seeing in these tissues. At this point in time, we don't actually know that very basic question and we don't know whether these side effects that we're seeing are the same as diseases that we see.

So for instance, if people develop diarrhea, is this the same as inflammatory bowel disease or colitis or is this something completely different? And so this is a very active area of research at UCSF and we're really trying to tease this apart. Again, trying to learn as much as we can from every person that we treat. The other component is we actually have a team of specialists that deal with these different side effects. This is a really new area in medicine. And so we have specialists that are focused in each organ that these side effects can arise and, we basically have a referral clinic to help manage these patients. So if you go onto our website, which is immunotherapy.ucsf.edu, there's actually a link there to our specialists who are focused on, helping to manage as well as helping to research why these side effects arise.

David: That's information that I can take back to the melanoma community and share with them because it's a big concern. I have two more questions if I could. First of all, I know you do some work with BioAtla and they're doing some interesting stuff. Could you talk for a little bit about conditionally active biologics? It sounds pretty interesting.

Dr Lawrence Fong: Yeah. So, we actually just had a publication on this about a month or two ago. The idea here is when you give an immune checkpoint inhibitor, these antibodies basically go throughout the body. And in fact, when we use a radiographic imaging to look at the distribution of these antibodies, they are in the spleen and in the lymph nodes and in the lungs and in the liver, they're all over the place in addition to being in the tumor. And so the idea is rather than having these antibodies turn on the immune system everywhere in the body, could we actually direct that to the specific tumor site? And in doing so, could we actually get these to work better. And what we found in preclinical models is indeed you can actually not only maintain antitumor responses, so you can basically shrink tumors in these preclinical models, you can actually avoid some of the side effects in these preclinical models. And so, this company as well as others are thinking about actually moving those into the clinic and I've actually moved them into the clinic. And so that's another area that I would really suggest staying tuned in that, if we can really improve that therapeutic index, by either maintaining or improving clinical responses but avoid some of the side effects that would also represent a significant advance.

David: Okay. Last question and be oddly enough, I'm actually teaching some of this to my high school seniors in biology. As we speak, they have a test tomorrow. I'm here in Michigan, I'm a Michigan State Grad and I live in Michigan and I follow Dr Nubick's (unclear 26:51) work on the RNA transcription inhibitors. And I know you might not be comfortable talking about somebody else's work, especially so early on, but could you explain it for us a little bit and then talk about maybe some comparisons between its potential versus some of the work that you're doing in immunotherapy?

Dr Lawrence Fong: Well, our RNA is basically the message with which cells produce proteins and work. And so it basically gives a cell a program on how to work. And as you might imagine, targeting RNAs through different approaches really allow us another way to reprogram a cell. And so if you think about a cell as being, the computer or the RNA represent the software. And so I think, there are many ways now that people are looking at using RNA so that you can reprogram the cells that can either help to stimulate an immune response or it could serve as means by which you could actually turn off pathways that you think might be impacting the immune response. And so it's really a wide open field here and another exciting area that hopefully we'll see developing into therapies that hit the clinic.

David: Thank you very much Dr Fong. I'm going to pass it along to whoever's next on the panel. I appreciate it.

Priya: Thank you David. Next we have Joel Nowak, Joel is founder of Cancer ABCs and a survivor of five primary cancers. Joel, you are live.

Joel T. Nowak: Thank you so much, Dr Fong. We appreciate your presentation. I actually want to do a little bit of a follow up question to David's excellent question about side effects. Many people have autoimmune illnesses, arthritic conditions and things of that order. And if you're taking off the brakes of the immune system, isn't that going to create a conflict or a problem for people, should people with autoimmune illnesses even consider some of these immunologic therapies?

Dr Lawrence Fong: Oh, that's also a terrific question. The clinical trials that we perform on folks with these immunotherapies exclude patients with autoimmune disease. And, so as a result, information that we have from these clinical trials on autoimmune disease patients is lacking. What's happened as these therapies are now FDA approved is that, physicians can now decide how best to use these drugs and whether or not trying these treatments in folks with autoimmune disease might be appropriate. This is something that is really evolving now and it is evolving in medical practice and I think it's critically important for patients to really consult with their physicians to see whether or not it would be appropriate because the concern is that by removing the brakes you would potentially make the autoimmune disease worse. Now, if an individual has a distant history of autoimmune disease that is not active, that might be a different scenario than somebody who has active autoimmune disease, at the time that they also need their immunotherapy. But I think, this is really a critical question that individuals need to take up with their physicians on a case by case basis because again, we don't have a lot of experience based on the clinical trials done thus far.

Joel: Right. Thank you. And just to make sure it's clear and I think you said it, but still that if anyone does have an autoimmune illness or is concerned about that, they need to really make sure that their doctor knows about that. And that enters into the conversation. Also if I would ask you if you could clarify something. Oftentimes I find when I talk to patients, there's some confusion under the concept or the word vaccine when it comes to immunologic therapy. Most of us or many of us think of vaccines is something that'll stop the disease. But you mentioned that Sipuleucel-T is the vaccine, but it's only given to men who already have prostate cancer. Could you clarify that a little please?

Dr Lawrence Fong: Yeah, so most of the vaccines that we use in medicine are prevention vaccines and so, the pediatric vaccines for measles as an example – these aren't to treat measles. It's actually to prevent individuals from getting that infection. So in the context of cancer, we have not gotten to that point of giving an immunotherapy that's targeting the cancer to prevent the development of cancer. There are some vaccines of viruses such as the hepatitis virus as well as a human papilloma virus. People who have chronic infections with those viruses are susceptible to liver cancer, to cervical cancer and we have those infectious disease vaccines. But we really don't have a cancer vaccine now that targets the actual cancer cells before a patient develops it. And so this is where the Sipuleucel-T that we've talked about that is a vaccine.

But in this context we're using it not to prevent prostate cancer, but to actually treat the prostate cancer. And as you might imagine, administering a vaccine when a person already has the disease, maybe a bit more challenging. And so this is why that vaccine is being studied in combination with other immunotherapies, but also new vaccines are being studied that are also trying to trigger immune responses. I think the other element is rather than giving these immunotherapies to people with metastatic cancer, that we should actually administer these vaccines earlier to people with more limited disease. And so in fact, that's what's going on now with Sipuleucel-T where men with localized prostate cancer are getting that vaccination as part of a clinical trial. But I think this is something that hopefully is vaccines gain more traction. We'll see them being studied in earlier stages of disease.

Joel: Thank you so much. Priya, I think I'll go ahead and let somebody else jump in at this point. Thank you so much for your answers.

Priya: Next in the panel is Amy Marash. Amy is a stage four colon cancer survivor and a retired TV camera Bowman. Her book of full colour cartoons and drawings about her cancer experience titled: Cancer is SO FUNNY is available on Amazon? So Amy, you are live, please ask your questions.

Amy Marash: Hi. Yes, thank you very much. And Doctor Fong, thank you so much for coming on the show and I'm really sorry the new therapies came too late for your father, but I'm glad you're working on them. I guess I'm particularly interested in the patient's experience and the caregiver experience. And so, you said right at the outset this has been a very wild ride and I assume you mean not only for clinicians but for patients and family and families. But I just like to offer from my perspective, I was recruited for clinical trials in quite a while ago in 2009 when I had active cancer and 2010 when I was in remission. But at the time I was so overwhelmed by my cancer diagnosis that I really did not understand the trial and I know how to read.

Amy: I'm not a real good listener, but I absolutely didn't even realize till I was halfway through the trial that I might be receiving a placebo and my particular trial, and I'm sure it was explained to me, but I didn't know it. And so I guess what I'd like to ask you is what kind of support do you give your patients who are considering entering a clinical trial, about the risks and costs and benefits of participating and do they have a patient advocate or someone to help them choose and should they have treatment when the success rate is small, should they travel for treatment? And personally, I know they told me that my experimental drug probably wouldn't benefit me, but I didn't believe that. And so what do you do? Is there any independent person who would help a cancer patient and evaluating is this trial for me?

Dr Lawrence Fong: That's also a really great question. And you're absolutely right. When I talk with our fellows in the clinic as we go to talk with a patient, I tell our fellows that the patients are really gonna remember if you're lucky, a third of what we're actually gonna talk about. And so this is critically important, to repeating critical points, including, if it's related to a clinical trial, but really spending the time to make sure that questions are answered. And so within our cancer immunotherapy team, it's not just an individual physician that would be interacting with a patient. It's really a team that includes a research coordinator, a research nurse, a research nurse practitioner, navigators within the clinic to help with all the different processes and things to consider on the clinical trials including financial implications.

With regards to having advocates, I think that's a really great idea. At UCSF, what we do have are support groups, where people from the community, basically participate and share their experiences and that sometimes this is a forum where people can present the different options. But I think, the critical part is when we convey all this information again, we need to really take the time and really need to emphasize those critical elements that you highlight. And, this is something that especially with the complexity of these immunotherapies, we're really giving people were caring for, a crash course in immunology, in addition to everything else. And so it's really making sure that everybody is aware of what we're doing and what the risks are. And so I hope that answers your question.

Amy: Yeah, it's a great, I mean, I appreciate it, I would add to that that, I mean, I love that you said they remember a third. I never batted a bat eye. I mean even when I go for checkups, I don't bet that high, but it's a great start. And I did work in a cancer center for about four years doing arts in medicine and I found that, and this is an NIH majorly funded cancer center. Many of the patients had talked to the navigator or the social worker on their first day of diagnosis or their first day of infusion or whatever. And then when they kind of got their heads together and got sort of used to dealing with their situation, there was no, many weeks later then, their consciousness would come awake and that, that have some questions.

So, I think maybe, if you think of a cancer center as a money making enterprise, you know how much money is going to go into the patient experience. I mean, I know that's not up to you, that's up to administrators and, and I appreciate your efforts in educating people. And you're right, my cancer was colon cancer and there's a phenomenal forum called Colon Club, that you can go online and listen and read and you can login and register. You can just read around on that site. And there's a lot of very, very, very informed, I don't know what you call them – posts or threads about immunotherapy. Anyhow, I think that was more or less, let me see what I wanted to ask.

Dr Lawrence Fong: Amy, to your point about the patient's experience. One of the things at UCSF is we have a new cancer clinic building that is opening in the next few months and, from the get go that building was purpose built really around the patient experience exactly as you're describing. And as you know, for folks that are receiving cancer care, you spend a lot of time within a clinic receiving treatments or waiting and part of that building and a lot of the space is dedicated for a patient so that they can spend their time either learning about their disease or learning about new treatments or spending their time in other ways that they choose. But I think, your point about focusing on what people experience is, is really a critical one. And I think certainly the cancer centers are changing that way in this new building is really with that in mind.

Amy: That is great to hear. I mean that, it's really great to hear and I appreciate that. I guess for you, I would ask what the challenge would be when you can't actually, you don't actually know the risks. In other words, you maybe will try one of these immunotherapies with a patient that looks like it might be helpful and then, maybe do you have enough data to even be able to tell someone and I know it's very individual, but this sort of your mileage may vary, well this might work for you, but it might immediately do that to you or two years down the road it might do some other thing.

Dr Lawrence Fong: Yeah. These are all things that when people come to learn about the clinical trials, we offer, we try to do the best we can, in informing folks of the risks. But as you point out, sometimes this is the first time a treatment's actually gone into a person. And in those situations, we try to use the science and the preclinical data to give us a sense of the potential risks that are there. But everybody who goes onto the trials, has to understand that there is going to be unknowns as part of the trial. That's the very nature of the clinical trial and this is where having our team be hypervigilant for things that are out of the ordinary is critically important in that, we might recognize and you new side effect. And that's something that we need to be very vigilant about.

Priya: Thank you Amy. And thank you Dr Fong. We are going to just open this up for some audience questions now. I've been receiving emails since we started off show we are going a couple of them. We probably, take a look at a few others as well? One of our listeners wants to know that, she says she read recently that intake of probiotics makes immunotherapy less effective in cancer? Is this true?

Dr Lawrence Fong: The area of probiotics and the microbiome are really a hot area of research right now. The thought is, with probiotics you basically alter the bacteria that are in your body, including in your gut. And, there's an emerging data that shows that depending on what types of bacteria are in your gut, that may actually alter your chances of responding to an immunotherapy. And as your listener points out, there also is some data that people who've received probiotics actually have a lower response rate. I think this information needs to be a confirmed and there needs to be more people studied in order to determine these effects. But I think in the meantime, since there's so much that we don't know about the probiotics and how best to modify the microbiome, I would recommend to your listeners if they're interested in this type of an approach to really do this in the context of a study.

Because, sometimes even though people might think probiotics as a whole might be a good thing, this is an example where it may not actually be a good thing. And, we'd really want that to be formally studied and documented. And so again, my recommendation to the listeners would be if you're interested in probiotics or changing your microbiome to really try to participate in a study so that it can be looked at and there's a rationale behind what we're doing.

Priya: Thank you Dr Fong. The next question is are there immunotherapies are working for colon cancer that has metastasized to other organs? And if so, what are they?

Dr Lawrence Fong: Well, with regards to colon cancer, we now know that colon cancer can come in a few different flavors. And there's one flavor of colon cancer where there's alterations in the DNA repair mechanisms and we call that MSI high colon cancer. For those individuals, we have an anti-PD-1 antibody that's FDA approved and has a very high response rate in the setting of colon cancer. Unfortunately, that's a minority of folks. And so the majority of folks will not have that mutation or alteration in their cancer. For the

majority of folks that don't have MSI high, right now this is a very active area of research with regards to immunotherapies. And so there are vaccine trials and bi-specific trials and other trials that are going on in colorectal cancer. And so this would be something where we don't have the answer yet, but again I would stay tuned as these newer approaches are underway and give us a sense of whether or not they're there working for people who don't have MSI high colon cancer.

Priya: Oh, okay. Thank you. Doctor Fong. Now we have David with another question. Yes. David please go ahead.

David: One, one more question, Dr Fong. I've read a couple of your papers and a couple of the abstracts and I know that a lot of your work focused on prostate cancers, that's your natural field of interest. Well, my natural field of interest as a melanoma survivor is melanoma. And I'm curious how, kind of explain to the layman how we can extrapolate the immunotherapy that you've been working on for over the years with prostate cancer. How we can extrapolate that into melanoma care?

Dr Lawrence Fong: Yeah. So, melanoma and prostate cancer are very different cancers. As you're aware, melanoma arises in areas that often are sun exposed. And as a result, there's a lot of mutations that are there within that cancer. In contrast, prostate cancer actually has a very low number of mutations. And so as result, the pool of targets that the immune system can see is actually less than it is in melanoma. And so, with regards to thinking about these two diseases, we really need to think about how the immune system is actually seeing these cancers on their own. And so in this context an immune system might be better able to see a melanoma rather than a prostate cancer. I think the other component is we know that the prostate and prostate cancer are very immunosuppressive and this really creates a challenge if even if you have an immune cell that can see the prostate cancer when it gets to the cancers, when it gets to the tumors, it can unfortunately get shut down by a lot of different mechanisms besides PD-1.

And, some of these mechanisms actually are more than likely also relevant in the context of Melanomas, particularly those melanomas that are resistant to our existing immunotherapies. And so I think this is where some of these observations that we can learn in prostate cancer may actually help guide us in other cancers that are more difficult to treat or are resistant to our immunotherapies. And the hope is that some of these might be applicable to other or difficult to treat cancers such as colorectal cancer as we talked about as well. And so, this is again another very active area of research and hopefully we'll get a better picture of that as we learn more.

David: Thank you Dr Fong. That was very interesting. I appreciate that.

Priya: Thank you. David. Dr Fong, we've received quite a few questions, people wanting to know the status of cancer immunotherapy therapies in breast cancer?

Dr Lawrence Fong: Yeah, so breast cancer has been another disease that has been challenging with regards to the immunotherapies and again as we talked about in colorectal cancer, breast cancer actually comes in quite a few different flavors. As it turns out, we now have an approved therapy for breast cancer, which combines an anti-PD L1 antibody called Atezolizumab with chemotherapy and for women with that specific flavor of breast cancer, particularly if their breast tumors have this PD L1 protein in the tumor, using this immunotherapy is now actually a approved for that breast cancer. For other flavors of breast cancer ee do see some responses with these anti-PD-1 antibodies, but those rates of response are not very high. I think this is where a lot of interest in the field is thinking about combinations that could enable these immunotherapies to work.

I think another area of excitement is actually using these immunotherapies earlier in a breast cancer. And so in research that actually pioneered at UCSF with Laura Esserman's group and the I-SPY program, immunotherapies have actually shown to have a good activity when given prior to surgery for breast cancer. And so this would argue that perhaps giving immunotherapy earlier in breast cancer may actually also significantly improve our response rates. And so now there are clinical trials that are focused specifically on

that. And so that's another area that I think we should see significant progress over the next few years.

Priya: Thank you. Dr Fong. We just have time for two more questions and then we can wrap up for today. The first one is, is there a movement to break out of the traditional data collection for clinical trials to allow for patients who might not qualify for a trial to try a drug without it "corrupting" a data set, thereby allowing for more experimentation?

Dr Lawrence Fong: Yeah. No, this is a very challenging question and this really speaks to cancer or not being one disease but really hundreds and thousands of different subtypes of cancer. And unfortunately, if you have a rare cancer or a rare variance of a cancer, you may not qualify for a clinical trial. And at this point in time, the way clinical trials are approved and run. We have to be able to define the specific patient population that we're treating on those trials. I think the hope is that as we get more therapies approved and available within this treatment toolkit that I alluded to, we may be able to customize treatment for people with rare cancers. But, at the present time we don't have enough of an understanding to help guide us in selecting treatment for many of the cancers. And unfortunately the numbers of drugs that are now approved in that tool kit is still a fairly limited, but the hope is that as we really learn more about the different cancers and how they may be immunologically similar to others, I think that would really give us an opportunity to broaden out these immunotherapies to these rare tumors.

Priya: Thank you, Dr Fong. The last question and then it's a wrap for us today. The listener wants to know, aside from the scientific challenges, what are the top barriers in bringing cancer immunotherapies to patients?

Dr Lawrence Fong: Well, this is also a really big question. I think the barriers are many. I think part of it is access to these immunotherapies and clinical trials. A part of that is the cost even for the approved immunotherapies are quite substantial. That's also a very broad issue that is hard to address in 30 seconds. But I think this is something that immunotherapy in my mind is here to stay and the hope is that even despite these barriers, it'll be available to more and more patients as we address these barriers.

Priya: Thank you Dr. Fong. As we continue to learn much more about how immunotherapy works and about the immune system as a whole and develop a better understanding, I think it may make it more likely that we will discover new immunotherapies that could potentially be used to treat all cancers. So Dr Fong, thank you so very much for sharing all this information on the latest immunotherapy treatment options in research with us today. David, Joel and Amy, thanks a lot for your participation and bringing the patient's perspective into the discussion. Mike Scott who was part of our panel today could not make it, he has just emailed apologizing because he actually got caught in a traffic accident. Luckily, nothing untoward has happened. It's just a few scratches. That's what he said. So he wanted to apologize, Dr Fong for not being here today, and to the panel as well. And so we thank UCSF Helen Diller Family Comprehensive Cancer Center and the audience for all the support today and this talk will be available on curetalks.com. So please visit our website for details on upcoming talks. Thank you everyone and have a great evening. Thank you Dr Fong. Thank you.