

Welcome to Yale Cancer Center Answers with your hosts doctors Francine Foss and Anees Chagpar. Dr. Foss is a Professor of medicine in the section of Medical Oncology at Yale Cancer Center and is an internationally recognized clinician and clinical researcher. Dr. Chagpar is Associate Professor of Surgical Oncology and she is the Director of the Breast Center at Smilow Cancer Hospital at Yale-New Haven. Yale Cancer Center answers features weekly conversations about the most recent advances in the research diagnoses and treatment of cancer and if you would like to join the conversation, you can submit questions and comments to canceranswers@yale.edu or you can leave a voice mail message at 1-888-234-4YCC. This week you will hear a conversation with Dr. Lieping Chen. Dr. Chen is a United Technologies Corporation Professor in Cancer Research and Professor of Immunobiology, of Dermatology and of Medicine at Yale School of Medicine. Here is Anees Chagpar.

Chagpar You are clearly very accomplished. You are Professor of Cancer Research, Professor of Immunobiology, of Dermatology, and of Medicine. Tell us about what you have been doing in terms of your research that is making changes in the world of cancer?

Chen I work in a field called cancer immunology. I have been working in this field for over 25 years and started as a graduate student. The field has evolved quite a bit in that time. In the beginning it was more about understanding how the immune system interacts with cancer, meaning how the immune system tries to attack the cancer and then how cancer counter attacks, basically trying to shut down the immune system. So those are the key things about cancer immunology, to understand how the immune system can attack the cancer, how it can efficiently attack cancer, and then you design specific therapeutic approaches. I would say this entire field started in the 1950s. And now we do know a lot about how the immune system tries to attack cancer, for example, a lymphocyte will come to the tumors, they will recognize the tumor imaging and they will try to kill the tumor cells. I would say in the last 10 years, we have learned more about how cancer tries to escape from the immune system. So the cancer obviously is very flexible. Actually, during the growth, they come find lots of different ways to escape from the immune attack, for example, they will specifically select some mutants, mutant means different types of tumor cells, and they do not express a particular target and in that way they will escape from the T cell attack because when the T cell tries to recognize the target, before killing them, if this target is missing, then they would not be able to kill them. Also the tumor cell expresses lots of molecules which will shutdown the lymphocyte activities. I think in the last 10 years we started to understand more in this molecular basis or cellular level of how the cancer cells, how to counter attack the tumor cells, so based on that knowledge, we can obviously design smarter ways to block those mechanisms. I would say the field has a robust design of a variety of different cancer therapeutic strategies starting with a couple of areas, and one is called a cancer vaccine. A cancer vaccine is

based on discovery of cancer express particular protein, which is either different, which is made up by mutated genes or they are over expressed, a normal cell, has a very low level, or they should not be in this particular location, a cancer cell can do that. Now those particular proteins made up by cancer could be

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recognized by immune system by the lymphocytes. Now these lymphocytes, once they recognize them, then based on this knowledge you can make more energy. You can artificially make recombinant protein, and then make them more efficient as a stimulator of lymphocyte. So that is one way which is basically the principal of a cancer vaccine. You isolate the particular tumor with the energy. Then you formulate it in a particular way to make them more efficient to stimulate the immune system, so that is the cancer vaccine approach. Second approach, which is also now ongoing is that you can isolate the lymphocyte from the body and especially isolate those from the cancer site. There you identify those lymphocytes as these specifically recognized energy. You can artificially expand those lymphocytes, increase the number, and then fuse them back to the patient as therapy called adaptive immunotherapy. That strategy also has some success because once you transfer a lymphocyte into it you can see the tumor starts shrinking and you can see that sometimes the effect can be a long lasting. Now a cancer vaccine, and this approach, both have been going on for probably 30 years, I would say, with limited success, and one of the issues efficacy, most of the time we are dealing with late stage patients. Tumor volume is very large already. Now with this therapy sometimes you can see the tumor transiently down the volume, the volume is down, however, the effect is not very durable, meaning they are not long lasting. Now this has been an issue in terms of immune therapy. Another issue is that sometimes we do see lots of active lymphocytes in the blood, circulating the blood, after adaptive transfer or after cancer vaccine, however, with this active immune system, or immune cells, in place, the tumor still grows. So this has been a confusing issue to the field. Why there is active immune response, in the presence of active immune response, but still the tumor is actively growing. I think now we understand it a lot better. Because more recently this molecular basis, the molecule discovery of some particular suppressive mechanisms in the cancer site. So, now we explain why this previous approach does not work well, because the immune cells activated by the vaccine or adaptive transfer, they migrate to the tumor site. They are ready to kill the tumor cell, however, this tumor develops its own strategy very quickly. They overexpress a particular molecule and shut down the lymphocytes in the tumor site. These findings actually explain why this overall stimulation of the immune system is not going to work that well. It is almost like you try to train more soldiers, however, you do not give them proper weapons. You just send more soldiers to attack to the bunker and try

to attack. Then there are more lymphocyte like soldiers go to the tumor sites, however, they are facing this counter attack from tumors. So these soldiers are not ready for that, so they very easily die in the tumor site. So this overall strategy now has a problem. I think only in the last few years now we understand there is a molecule, for example, there is a molecule called B7-H1 or also called PD-L1, this molecule is overexpressed by cancer. Now they can bind to PD-1, program death one, and this is the receptor of this molecule on T cells. Once T cell activate, T-cells come to the tumor site. Now these tumor cells express this PD-L1, they bind to PD-1 and they shut down the T cells. So this is one of the reasons these large T cells come through a site, but before they can function properly they die or they hold there, they lost function and they are paralyzed, so our therapy design was, we can design a specific monoclonal antibody which binds to either PD1 or binds to PD-L1, which blocks the interaction of this molecule so it blocks the communication of this signal delivery, then you clearly see this expansion of T cells,

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T cells become much more active in the site of tumor, but not in the whole body everywhere. So these T cells then become very active because they do not have such inhibition around so they can actively attack the cancer and they survive very long. So I think this therapy is distinct from the other types of immunotherapy before because it is much more specific in a tumor site rather than systemic activation. So we just described a couple of approaches, vaccines or T cells transferred and a couple of years ago there was a drug approved called anti-CTLA-4 which is an inhibitor on the T cell surface, however, this inhibitor is not tumor micro-environment specific, it is in the whole body. So after you block that inhibitor then you get T cells around the entire body. You have lots of T cells activated including some auto-reactive T cells. That then causes quite a bit of autoimmune toxicities. In contrast, anti-PD-1 or anti-PD-L1, we do not really see a lot of auto reactivity. The reason is because this is more focused manipulation of tumor site rather than entire body. So that I think has made a lot of difference. Because of this therapy we have learned a lot. We know that immune therapy has to be focused on tumor site ideally, we call tumor microenvironment, and have minimal effect on the other parts of body and that would be the more ideal type of therapy. So this is what we have learned and now we are now actually actively working to see if we can find a more such approaches to try to get better, more efficient and less toxic therapies.

Chagpar Wow, that is exciting work. We are going to pick up the conversation and learn more about cancer immunotherapies and new treatments for cancer with our guest, Dr. Lieping Chen right after we take a short break for a medical minute.

Medical

Minute The American Cancer Society estimates that the lifetime risk of developing colorectal cancer is about one in twenty and that risk is slightly lower in women than in men. When detected early, colorectal cancer is easily treated and highly curable and that is why men and women over the age of 50 are advised to have regular colonoscopies to screen for the disease. Each day more patients are surviving colorectal cancer by accessing advanced therapies and specialized care, which is giving survivors more hope than they have ever had before. Clinical trials are currently underway at federally designated comprehensive cancer centers, like the one at Yale to test innovative new treatments for colorectal cancer. New options include a Chinese herbal medicine being used in combination with chemotherapy to reduce side effects of treatment and help cancer drugs work more effectively. This has been a medical minute brought to you as a public service by Yale Cancer Center. More information is available at yalecancercenter.org. You are listening to the WNPR Connecticut's public media source for news and ideas.

Chagpar Welcome back to Yale Cancer Center Answers, this is Dr. Anees Chagpar, and I am joined today by my guest, Dr. Chen. Before the break we were talking about cancer immunology and Lieping was laying out for us the history of this incredible field and where it is has come over the last 30 years. He has been doing a lot of really exciting work at Yale, looking specifically at targeting the immune system- tumor interactions at the tumor site. Lieping, I want to take a step back just for

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a moment to look at the bigger picture. You talk about this war with tumors and the immune system, if we have functioning immune systems, why do we get cancer? I know that some people have suppressed immune systems, for example, people with HIV are more prone to getting cancers, and with Kaposi sarcomas, and a lot of that we thought was due to a lack of a functioning immune system, so why is it that people who have a functioning immune system get cancer?

Chen That is a very good question, there is clear evidence that if you have immune suppression then particular types of cancer are higher. However, we know that those cancers are specific types of cancer, for example, as you just mentioned, a virus infection related cancer, those are clearly much higher in the immune suppressed patients like with renal transplantation when you give immune suppression, they clearly have a higher level of a couple type of cancers. So the issue is then, why if there is clearly an immune system there, is that tumor still growing? This is a little bit of theoretic speculation because this is a human, so you cannot really perform experiments to answer

that question. So we have to be speculative. There are a few theories like this. One theory is from a long time ago, in the 50s, talking about the cells in human beings and that they mutate all the time, and they have some mistakes in the genetic recombination. So then in theory, the mutation happens all the time, so the cancer cell will come out in the body in one normal individual frequently. So, that is kind of a scary theory. Then the explanation at that time says, why then is our cancer incidence low, overall it is low, 1 out of 10,000, why is that? It is because active immune systems suppress most of that tumor growth. So you have very rare, few mutations that hit in the critical site or you have multi-mutations and the immune system just doesn't have enough time to suppress them. So that is one theory. However, that theory is now being challenged dramatically because you can have a patient with a suppressed immune system, for example in the transplantation patients, and they only have some very rare cancer come out. Not all cancers come out, say for example, you have a patient with long term use of an immunosuppressant drug in the renal transplantation, they usually do not get lung cancer. They do not get breast cancer, they do not get prostate cancer, what they get is a viral related cancer like EBV related lymphomas, or they can get cervical cancer. So those are all viral related, cervical cancer is related to the human papillomavirus, so that is kind of against the theory. In common cancer, what is the origin of this common cancer? That has not been accurately solved. We know a little more about it, is in solid tumors, common cases, probably less than 5% is related to genetic mutations. So you have breast cancer that is related to BRCA1 and BRCA2 mutations, but those are very rare. So the majority of the solid tumors, or common cancers, we do not really know why the immune system cannot get rid of them in the very early stage. That is still under study and there is a lot of theory behind that. I would like emphasize, one key issue is the immune system, to control the early cancer and the immune system to try to establish in late stage patients, those large tumors are very different. In the early stage of cancer the immune system is very healthy and also there are different types of immune systems, so the innate immune system, which is mostly in nature killer cells, macrophage, neutrophils, they are a major force to control those small differences, meaning it is an early stage tumor. Lymphocytes are called adaptive immune system. They only deal with much larger problems, when you have tissue damage, or when you have

22:33 into mp3 file http://yalecancercenter.org/podcasts/2014_0309_YCC_Answers_-_Dr_Chen.mp3 fevers you have lots of damage in the tissue, then those systems will come out. So one theory is that innate immune system might not be very powerful in the beginning, or can easily be fooled by the cancer. So that is why they are not powerful. So early cancer can reach a certain stage and then start to grow. Now in late stage patients, that we are dealing with all the time in the clinic, which is the tumor has already grown out, they have already tried to escape from the immune system. So one mechanism I just described is that these cancer cells, they can steal some of the normal suppressive mechanism

to amplify and then to kind of seal themselves from the attack. For example, PD-L1, which is over expressed by cancer cells, is not unique for cancer in the tissue infection or tissue damage. This molecule also comes out. This is the body's natural response to the damage. They try to control that area, try to shut down the inflammation and not let this damage get too big. So that is the physiological function. Now cancer cells steal that mechanism and amplify it, make it very big, and make a larger expression. Then these mechanisms become very powerful and shut down the lymphocyte response, and cancers use a variety of different kinds of these mechanisms and some of the PD-L1 is the system I describe is more focused on cancer site. There is a TGF-beta, for example, that is released by cancer cells. They can shut down immune response. However, the TGF-beta is more of a systemic effect and they can be released into blood and they move to different organs to have effect. So cancer can develop a variety of these mechanisms to adapt to the environment. They want to survive. So this is what they try to do. For us researchers, all we need to do is to identify those mechanisms to see what is the particular mechanism operating in the tumor site. Something difficult for the cancer biologists and also for cancer therapeutics is it appears that different types of cancer, might employ different types of suppressive mechanisms and use different mechanisms to attack the immune system, and that is what makes it difficult because say you discover one mechanism, this might only operate in one type of cancer but not others. For example, with TGF-beta therapy, some cancers release a ton of TGF-beta to suppress immune response, for example, in head and neck cancer they release a lot of TGF-beta so then the therapy will target and will work well. However, with other cases, for example melanoma, they do not release lots of TGF-beta, so this kind of therapy will not be effective. Interestingly, going back to this PD-L1 therapy, it appears to be quite broad for cancers that use this mechanism, however, again it is a fraction of the cancers. We know the therapy works in about 30% of late stage lung cancer, in about 40% of melanoma, in about 40% to 50% of renal cancers, and now it seems like 30% to 50% of bladder cancers, but it is not 100%. Why it is not 100% is because this molecule is not expressed in those patients who do not respond, that means those patients are resistant to this type of therapy, they use another mechanism, they use this resistance strategy, so that is what we need to find out. This is what we are working on now, if this patient responds to this therapy, to anti PD-1 therapy, how did it work, if this patient is resistant, what other types of mechanisms are operating and so this is our main focus right now, to figure out this problem.

Chagpar Is it the case that you can tell, based on the biopsy of the tumor, whether or not it expresses PD-1? Whether or not this therapy will be effective and whether this interplay occurs via that mechanism?

28:16 into mp3 file http://yalecancercenter.org/podcasts/2014_0309_YCC_Answers_-_Dr_Chen.mp3 Chen Yes, this is going to become a standard biomarker. In fact, Genentech is a company actively developing the anti-PD-L1 antibody and Merck, another company, also developed an anti-PD-1 antibody. They already use screening of PD-L1 expression on the cancer cells, on the biopsy specimen, as the recruitment criteria, meaning if this is only positive on PD-L1 expression it will be recruited to the trial. If it is negative, it will not be recruited. However, there is a company like Bristol Meyer Squibb and they are still doing non-selective patients and they recruit all comers. So this is the way to increase efficacy, by this preselecting marker. Obviously this is just one on marker and we are also now working with lots of teams to try to work out the other markers also.

Dr. Lieping Chen is United Technologies Corporation Professor in Cancer Research and Professor of Immunobiology of Dermatology and of Medicine at Yale School of Medicine. We invite you to share your questions and comments with Dr. Foss and Chagpar. You can send them to canceranswers@yale.edu or you can leave a voicemail message at 888-234-4YCC. As an additional resource, archived programs from 2006 through the present are available in both audio and written versions at yalecancercenter.org. I am Bruce Barber hoping you will join us again next Sunday evening at 6 for another addition of Yale Cancer Center Answers here on WNPR Connecticut's Public Media Source for news and ideas.