

Welcome to Yale Cancer Center Answers with doctors Francine Foss and Lynn Wilson. Dr. Foss is a Professor of Medical Oncology and Dermatology, specializing in the treatment of lymphomas. Dr. Wilson is a Professor of Therapeutic Radiology and an expert in the use of radiation to treat lung cancers and cutaneous lymphomas. If you would like to join the conversation, you can contact the doctors directly. The address is canceranswers@yale.edu and the phone number is 1888-234-4YCC. This week, Francine and Lynn welcome Dr. Lieping Chen Professor of Immunobiology and Director of Cancer Immunology at Yale Cancer Center for a conversation about the discovery of new cancer treatments. Here is Francine Foss.

Foss Could you start off by telling us a little bit about your history and how you got interested in the field of immunobiology?

Chen I was trained as a physician/hematologist, and that is how I got started in the medical field. Early in my career, especially in clinical practice, I found that the majority of cancer patients, and this was in the 80s, had very minimal options for treatment. At that time, it was pretty much just chemotherapies, especially as a hematologist where we are dealing with leukemia and lymphoma literally every day, and that did not have, I would say, a perfect treatment in the 80s. So that made me want to be more on the research side looking for the new treatment rather than just practicing the medicine.

Foss Can you tell us how long you have been at Yale Cancer Center and where you were before you came here?

Chen I joined Yale Cancer Center and Yale School Medicine in January of this year, so it is less than one year and I came for Johns Hopkins University School of Medicine and Johns Hopkins Hospital. I worked there for about seven years.

Wilson You suggested a little bit about your interest in doing something else other than hematology with some of the frustrations in the 80s, but what specifically turned you toward immunology?

Chen Immunology, then and now, is one of the fields that is most close to the clinic. It is a basic science, however, the issues that immunology deals with, are highly related to how we understand the immune system and how we use the immune system as a way to prevent or to treat the diseases in 80s, so this is one of closest field I would say to medicine and now still is one area that is very close to medicine.

Foss Can you talk about the connection between immunobiology or immunology and cancer?

Chen The immune system obviously is very important and it is always there to either prevent or to control the diseases. Cancer immunology, in that aspect, is no different compared with the other

3:57 into mp3 file http://yalecancercenter.org/podcasts/2012_0108_YCC_Answers_-_Dr_Chen.mp3 field of immunology, such as microbial immunology or autoimmunity immunology. However, there is some uniqueness to cancer immunology because now that we understand the immune system, it is quite complicated and it can be manipulated by cancer in the beginning so we have to understand from the beginning how the immune system is being ordered and then later how we can use the information to be useful to control the cancer growth, or to even, in the late stage patient, where the immune system is largely compromised, how can we restore that and make it a useful weapon against cancer?

Wilson So our listeners understand, can you talk for a minute about the basic immune system, basic immunology, what that is in fighting infections or foreign antigens? What is the basic role of the immune system in humans?

Chen In most cases, the immune system operate on a fairly low level because every day human beings are exposed to the environment, exposed to different germs, and different foreign material. All these things could hurt the body, so the immune system is always there. In most of the cases, they control the common cold or cuts, and just a low level immune system is sufficient for that. However, sometimes the disease persists or gets out of control, let's say you have an infection which is a dangerous bacteria or a dangerous virus, the immune system has to play a large role. In cancer, the immune system plays a very critical role because cases develop usually very slowly, however, it is persistent and if you do not control them the tumor will definitely keep growing and then it would be out of control within a certain period of time. Now we understand the immune system is also ordered by cancer because in cancer they try to escape from immune destruction. They develop a lot of different mechanisms, so to understand these mechanisms and understand how the immune system is ordered has become a very critical issue in the field. In general, human beings do not have to have an immune system to live, for example, we have mice which are completely deprived of immune systems. They still can live, but they can only live in this sterile environment, but human beings are different. You have

to be exposed to the environment and you have to deal with the environment so that is why our immune system is always there to protect us.

Foss The basic concept with cancer is that when the cancer cell becomes malignant, becomes a cancer cell, that cancer cell potentially could be recognized by our immune system the same way say a bacteria is?

Chen Yes, the answer is absolutely yes, because in the last 20 years we found that every normal cell, when they transform to become a cancer cell, they make a protein, quantitatively or qualitatively, meaning they are quite different from the normal cells, so those could be recognized by the immune system.

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Foss So the immune system really is your first line of defense against cancer and you talked a little bit about how the cancer cells are smaller than the immune system and they find ways to abate the immune system, can you elaborate a little bit about that?

Chen Yes, cancer cell always try to escape from immune attack because, particularly in early stage disease, that is the only thing preventing the tumor from propagating. So the immune system, as we just mentioned is the first line of defense. In order to survive, the cancer cell change a lot of things to combat with the immune system, for example, the immune system will recognize a specific protein which is displayed by a cancer cell because in order to proliferate, to grow, they require specific nutrition, or they develop some particular pathway to make them grow much faster than normal cells. Those differences could be detected by the immune system. The immune system started to detect those proteins and tried to pick those cells up and kill them. Now the cancer cell, in order to survive, also developed different strategies to try to either get rid of the new cells completely or make them paralyzed, by the different strategies, including hiding this particular protein or mutating this protein. Then this way, they can escape from the particular immune system attack, so that is what is happening now. We found a lot of defects on the immune system when the patient develops a large tumor, so they already successfully escaped the immune attack.

Foss Is there any way to detect this earlier on, are there any ways or strategies that we can use to detect these malignant cells, say before the patient has a big tumor?

Chen This has been very challenging in the field for early detection of cancers. For some cancers we can do that now, some specific modification of the genes, genetic alterations or as particular protein or particular so called signature protein, we could detect it, but it is a very small fraction of those proteins or a fraction of the cancers that we can do that with now.

Wilson Obviously, this is very very complicated science but if we took a lung cancer tumor from another human, for example, and injected that into an immunocompetent human, would that tumor grow in the next persons' lung or is it likely that that person's immune system would immediately recognize those cells as foreign and then prevent the growth of that cancer?

Chen Obviously, those experiments could not be done, but the answer is probably not and the reason is that the cancer cell, just like normal cells, have a group of molecules called MHC, compared to the histocompatibility antigen which is the protein that distinguishes individuals, so everybody has a different set of this MHC molecule. That is the molecule which could make transplantation feel very miserable because they always try to overcome the MHC restriction and because this can be immediately recognized by the immune system it rejects those cells.

12:27 into mp3 file http://yalecancercenter.org/podcasts/2012_0108_YCC_Answers_-_Dr_Chen.mp3 Lynn So in the first patient, perhaps there is a mutation or a defect or something has happened in that person's immune system to allow this cancer to grow, maybe the cancer, as you suggested, has fooled or tricked the immune system or mutated its protein or hidden the protein, but in a different host its immune system may be different and strong enough to recognize this as the foreign target and eliminate that immediately.

Chen Right now that is what is happening in cancer treatment, when we develop one of the new therapies, usually we cannot guarantee they will work in 100% of patients because all individual differences generally make up a different environment, different modification or immune system and that makes immune therapy a challenge, same as the other fields and other therapies.

Wilson Talk us through the process of translating discoveries in the laboratory into the clinic. How does one go about doing that?

Chen Translational medicine is a field that is only being recognized in this recent decade. There is a lot of basic science going on to understand the body, to understand the immune system. There is also a lot of clinical medicine which continues to use the traditional methods such as surgery or chemotherapies or radiotherapies to treat the cancer, so the clinical medicine and basic research are often disconnected. The purpose of translational medicine is to see if we can utilize that basic information and design the new treatment.

Wilson Let's revisit some of those details in the second part of our show. Right now we were going to take a short break for a medical minute. Please stay tuned to learn more information about the discovery of cancer treatments with Dr. Lieping Chen.

Medical

Minute The American Cancer Society estimates that the lifetime risk of developing colorectal cancer is about 1 in 20 and that risk is slightly lower in women than in men. Early detection is the key, when detected early colorectal cancer is easily treated and highly curable. Men and women over the age of 50 should have regular colonoscopies to screen for this disease. Each day more patients are surviving the disease due to increased access to advanced therapies and specialized care. New treatment options and surgical techniques are giving colorectal cancer survivors more hope than they 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 and more information is available at yalecancercenter.org. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.

15:35 into mp3 file http://yalecancercenter.org/podcasts/2012_0108_YCC_Answers_-_Dr_Chen.mp3 Wilson Welcome back to Yale Cancer Center Answers. This is Dr. Lynn Wilson and I am joined by my co-host Dr. Francine Foss. Today we are joined by Dr. Lieping Chen and we were discussing new cancer treatments and immunobiology. Dr. Chen, in the first half of the show as we wrapped up you were starting to get into some of the details of translating discoveries, or basic research in the laboratory, and getting those discoveries into the clinic. Talk to us a little bit more about how that is achieved. It is actually a very complicated process, please tell us about that.

Chen Translational research is one of the fields that I consider very

critical for every cancer center. The laws of basic discoveries are made in the laboratories such as the ones at Yale University in our Department of Immunobiology which is one of the top programs in the world. Lots of information is being collected. We understand how immune systems function, how they work, we understand a lot of different mechanisms, and how to manipulate and control the immune system. The most basic scientists stop at that stage, they do not move forward to understand what happens in the cancer. They will stop and say okay, now we understand how normal immune systems work. However, the translational scientist will bring that a step further and examine those individual mechanisms or particular pathways or molecules in the setting of cancer or in other diseases. I will give you an example, say in lung cancer, the tumor is growing and then finally it metastasizes to the other one. Now, before the tumor can metastasize it has already developed a series of mechanisms which can escape from the immune control, so the immune system, to control the primary tumor has already failed. However, the new cancer cell moved to another part of body. They started to invade the immune system, but the immune system in that location might not fail yet. So to understand all these different locations and different mechanisms is very critical for differential treatment. You might not be able to treat one location, but you might be able to treat another one, for example. So to understand the entire system and also understand the localization issues, which have become very important, but the basic scientist usually will not consider that, they will just understand in general how the immune system operates, and then they will stop. Clinical scientists will usually do standard treatment. They will continue to do the standard treatment. So to get this translation going, first we have to understand the normal immune system. Number two is you have to pick the mechanism and carefully examine what happens in the cancer and identify the particular defect in the cancer or alteration in the cancer setting and then design an approach either to promote that deficiency, or to particularly remove some negative environment, some harmful situation, then find a way to design a therapy, so that distinguishes the differences of basic scientists and clinical scientists.

Foss Lieping one of the problems that we have in the clinic is that we treat patients with drugs and now we are using these monoclonal antibodies and these drugs that potentially could effect some of these immune cells as well, and we study the effects of those drugs on the tumor that we are

20:07 into mp3 file http://yalecancercenter.org/podcasts/2012_0108_YCC_Answers_-_Dr_Chen.mp3 treating or the leukemia and that we are treating, but do we really understand the results of a lot of these treatments on some of these immune mechanisms that you are talking about?

Chen Yes, this is a very interesting question. A lot of the time, when you design a therapy, or you design a particular drug, you might not understand the entire picture, you might not understand how this particular drug will do in the human, you might know a particular part, because all the information has come from a particular experimental model, or some animal study. So the knowledge we learn from those is obviously limited, but we use that to tell us, to predict, how it is going to work in humans. Sometimes it is impossible, but in most of the cases it will predict some of the things that are going to happen in the human, but probably not all of them, so that is why there are so many phase III trials that fail because right now the statistics are showing that in phase III, the drug will go through all the pre-clinical and the phase I, II, III, but still more than 90% of drugs fail. It is because there are lots of unexpected results that are found in the clinic.

Foss Should we be doing more studies in patient's to look at the affects of these drugs on the immune system?

Chen The answer is yes, because now we understand lots of models, either in vitro or in vivo, or the experimental system is incomplete or not perfect. So we need to do more human studies to answer those questions.

Wilson Can you tell us a little bit about the Cancer Immunobiology Program at Yale? What are some of the highlights and who is involved?

Chen The Cancer Immunology Program, in general, can be divided in to these three components. One is, as I mentioned previously, basic immunology. We have Dr. Richard Flavell, and Dr. David Schatz, for example, and they study very basic aspects of immunology to understand what kind of cells, which particular molecules, are involved in a particular defense mechanism. For example, Dr. Ruslan Medzhitov, many years ago, discovered a particular molecule called Toll-4, which is very important for the recognition of bacteria, and this molecule, after recognizing the bacteria, will trigger a series of biochemistry signals and can now host the immune system. It is part of the innate immune system. They are the very first line of defense, and then it can immediately control those bacterial infections. The second part of the Immunobiology Program is more on the clinical side such as Dr. Mario Sznol, who will use various reagents and/or other cells and give this therapy to cancer patients, and this is all based on the immune mechanism in immunology discoveries and the third part are people like me and Warren Shlomchik. We are doing a lot of translational research. Even in my own program, I consider myself a very basic immunologist because my main interest is to discover the order of immune cell communication molecules, how each protein

24:39 into mp3 file http://yalecancercenter.org/podcasts/2012_0108_YCC_Answers_-_Dr_Chen.mp3 is being used to communicate between the cells, but I do a lot of translational research, which is to understand this individual communication, then we always bring them to a cancer situation to see how we can translate them. So in general there are three components and this is all integrated. There is a lot of collaboration and integration of knowledge, so it is a very great environment.

Foss Lieping you had done some work that led to an immunotherapy that holds great promise for cancer and that's the anti-PD1 drugs. Can you elaborate a little bit about that? Tell us what it is?

Chen This goes back through a long history of discoveries, and we discovered one of the molecules called B7H1 which now is known as the PD1, and it is over expressed by cancer cells. As I mentioned previously, cancer uses a lot of these mechanisms, normal mechanisms, but twists them or alters them to escape from the immune response. This is one of the molecules for that purpose. Cancer over expressed is a molecule because this molecule, after binding to PD1, which is another protein that serves as receptor for B7 H1, PD1 is on T-cells. When T-cells are alerted to come to attack the cancer, then the first thing they are going to see is this B7 H1 on the cancer cell. Then B7H1 will give a signal to PD1 asking the lymphocyte to shutdown. So these mechanisms when we found out about them 10 years ago, first we found them in the Petri dishes, we found that a lymphocyte, once they encounter this molecule, they will be basically paralyzed. I think a critical step was taken about 10 years ago, when we immediately moved this to cancer a cancer setting and found that in human cases these molecules are overexpressed and they also do the same thing, they can shut down the lymphocyte. So this is how it started, we then designed the antibody to specifically block this interaction either in high PD1 or in high B7 H1 which is a lichen of the PD1 to block this communication or miscommunication, to rescue the lymphocyte around the cancer, so the advantage of this type of therapy is because molecules are specifically over expressed in cancer, the antibody, even when you give it systemically, it goes over all the body, but the effect is mainly on the cancer so that it avoids major toxicities, so that is what we are seeing in the clinic right now, the toxicity is very very low.

Dr. Lieping Chen is Professor of Immunobiology and Director of Cancer Immunology at Yale Cancer Center. If you have questions or would like add your comments, visit yalecancercenter.org, where you can also get the podcast and find written transcripts of past programs. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.