

Chagpar Good evening and welcome back to yet another episode of Yale Cancer Answers. I am Dr. Anees Chagpar, and I am joined tonight by my guest, Dr. Charles Fuchs. Dr. Fuchs is Director of Yale Cancer Center and Physician-in-Chief of Smilow Cancer Hospital. He is here with me tonight to discuss his new role at Yale Cancer Center and Smilow Cancer Hospital. Thank you so much for joining me.

Fuchs Anees, thank you for inviting me. I am so pleased to be here and to be joining the faculty and the community at Yale.

Chagpar Maybe you can start off by telling us a little bit more about yourself, your background and what drew you to Yale.

Fuchs Of course. I started my career as a medical oncologist focused on gastrointestinal cancers. And certainly, it's a very important area, gastrointestinal cancers are a major part of the burden of cancer and I was focused in part on developing new therapies, but at the same time early in my career, I was also interested in developing a research program focused on risk prevention as well as understanding the biology. So, we set up laboratories focused on all of those things and ultimately, we created a wide comprehensive program focused on all of those aspects of GI cancer, which we built over the years focused on novel therapeutics, focused on risk prevention, focused on diet and lifestyle. And that has been my background beyond being a practicing medical oncologist and have been involved in a variety of new drug discoveries. But when the opportunity was presented to me to come to Yale to lead Smilow and Yale Cancer Center, I thought this is an extraordinary opportunity, a fabulous place with great clinical enterprise, great science, and I am thrilled to be here.

Chagpar Charlie, tell us a little bit more about what does a cancer center director do exactly?

Fuchs It is a great question, and I would even step back and say what is a cancer center. And in fact, it is interesting because it reflects the history of what has happened through much of the 20th century as the federal government has approached cancer. During the many acts of legislation during the Great Depression, where the Roosevelt administration was just trying to build commerce and build all these programs to get people back to work, they created the National Institutes of Health and the National Cancer Institute. In its initial iteration, it was what we need to do better about cancer. Now that was 1939. But what happened that was transformative was in 1960s and 1970s when the National Cancer Act was passed in 1971 where they said, you know what, we really need to create beyond what we are doing in Washington in the National Cancer Institute, a Centers of Excellence focused on cancer within major academic centers that are really looking at the comprehensive effort of basic

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translational science, clinical science, clinical trials, outreach to communities and doing so in a way that integrates all of this, so that the basic scientists

are interacting with the clinicians to move novel laboratory discoveries into the clinic for the benefit of the patients. And really is what a comprehensive cancer center has to be. You have to have all of those components; the very basic molecular laboratory science, exceptional clinical care and clinical research, outreach and the bridges that can demonstrate all of that. Now, there are only approximately 49 comprehensive cancer centers across the US, Yale is one of them, and it was founded as a comprehensive cancer center I believe in 1974 and is really one of the leading centers both in terms of its exceptional accomplishment and its ability to gain funding from the National Cancer Institute. The Director, obviously oversees that, but as well sets the vision of what do we want that cancer center to be over the next 5-10 years, both in terms of the clinical operation, how we provide care to the patients but also how we support our basic research and hopefully move that into a direction that benefits patients.

Chagpar You know it is so interesting that you talk about the vision of where we are taking cancer. I think that is really becoming something that is more and more of a highlight, both in terms of an academic milieu but also to the lay public. If we think about the cancer moonshot and what Joe Biden has been doing, really this idea that we can accelerate discovery. Do you think that is really possible, and what kinds of things might comprehensive cancer centers do to facilitate that?

Fuchs I think that is really the major purpose from my standpoint of what a comprehensive cancer center does. Because here is what the problem was when this first nascent idea of a cancer center was created and where we are at today right? So, you could have a bench scientist at Yale who makes a fundamental discovery that impacts the biology of cancer, for which you might conceive of an idea that could lead to a novel method of prevention or treatment, but how do you do that? And that was really the problem in academic centers before these initiatives were created. What you really need to create is a core home for clinicians, clinical investigators, basic researches who are working together, who can then take that very nascent idea from the laboratory and figure out how to move that into a drug, into the clinic and really how to design clinical trials that take that laboratory discovery and leverage it to the maximum to its greatest benefit for the patients. And I would even say, if you want to take it in the reverse direction, which is when the patient is on that clinical trial, you want to collect specimens, blood samples, tumor specimens from that patient, return them back to the laboratory, so the laboratory can then say "we made this discovery, we are now testing it in patients, let us understand if it works the way we anticipate so we can refine it, improve it, make

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it even more effective." That is really what a cancer center needs to be because any pure academic center focused on only one component cannot really deliver the goods to ultimately make the lives of patients better.

Chagpar How do you do that exactly? It is all great to talk about this collabo-

ration, but you have scientists who are doing the science and they are living in the laboratory, and you have clinicians who are seeing patients every day and they are living in the clinic, how do you bridge them together?

Fuchs Some of it is organic frankly because I think the world has changed. When I was in my training early in oncology, like any good oncology fellow, after my first year of clinical training, I spent 2 years in a fundamentally basic laboratory focused on what make cells grow. I learned a lot about the scientific method, but I will tell you that was not that long ago, was in the early 1990s, but I would not say that there was a vision of how we would take any of those discoveries and move them into the clinic. Really, the measure was, did you get a paper published in a high-profile scientific journal and ultimately understand biology, which is what we wanted to do. But what I see today at Yale particularly is an interest of the basic scientist to have impact, to actually make what they are discovering, create better lives for patients, move something into clinical practice. I think it really is in part organic, as well I see the clinicians at Yale – clinical investigators, who really want to be engaged with laboratory investigators to understand what the new ideas are, knowing that we are making great progress in our delivery of care to the patients with cancer, but we need to do better, and if we are going to do better, we have to work together. That was one of the things that really attracted me to Yale, that sort of organic interest on both the clinical side and the basic laboratory side to work together to really leverage the extraordinary talent we have. But beyond that, I think what the cancer center can provide is programs and resources to help create the glue. For instance, if a laboratory investigator needs patient specimens to understand their hypothesis, let us say they have an idea of a new target for a drug in a cancer cell, but they really have to study in the context of getting specimens from patients. We want to make sure that there is this resource by which patient samples which are clinically annotated, meaning the history of the patient is part of that sample, the sample is then delivered to the laboratory so they can investigate it and then understand whether their target is really driving that cancer, and that should be done in multiple ways – simply taking an archived specimen of the tumor but as well having the ability to grow that patient’s tumor in the laboratory, the so-called living tumor bank, growing these cells either in plastic or actually in laboratory mice to really understand the dynamic process of cancer. So, part of what a cancer center needs to do, I am giving you one example, is to provide those resources by which what we do in the clinic can return to the laboratory and vice versa, as well to

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have the resources to be able to conduct clinical trials with novel agents, to do so in a safe and effective manner. So, beyond being a place where we provide exceptional, expert and compassionate care, which I believe Yale and Smilow do, but actually ensure that we have the space, the resources to conduct high quality, innovative clinical trials that can test those laboratory findings and obviously collaborate the findings with the scientists. So, really what a cancer

center needs to do is to create those resources, by which patients get exceptional care and at the same time can engage all the scientists, clinical scientists and basic scientists.

Chagpar You mentioned clinical trials a few times, which is something that we often focus on here on Yale Cancer Answers because one of the thought processes is that clinical trials actually are exceptional care. The patients who participate in clinical trials are not just helping to move the field forward but they are actually getting cutting edge care. Tell me more about how patients can engage in clinical trials and why that is important?

Fuchs This is absolutely a priority for us at Yale and at Smilow. We want to make available to all patients the cutting-edge clinical trials that are moving this field, I agree with you. I think that those clinical trials actually advance the care of patients because first the care is well defined, it is the highest quality, and what it does is, it delivers what would be care that would hopefully go beyond what is currently available through the standard of care. Now, certainly, there are plenty of circumstances for any individual patient where the best care is something not part of a clinical trial because it is an established treatment, it is the best thing we know, and for that particular patient, that is what should be delivered. And let us always recognize that the best care of the patient is what is best for that specific individual, be it a clinical trial or standard of care therapy, which is our approach. But in many circumstances, a clinical trial may be what is available clinically and actually then take it to the next level to provide some novel agent that will hopefully further augment the benefit we would otherwise see. So, I absolutely encourage patients to go on clinical trials. Moreover, I think many of the patients that come here are really looking for clinical trials. They are coming to our centers either in New Haven or our Care Centers across the state because they are really interested in getting access to cutting-edge therapies that would be beyond what would be available in any other center. So, this is what our patients want and that is what we want to deliver and we want to move the field in the process. But ultimately, let me emphasize, the role of clinical trials is to improve the care for the individual patient as well as for the larger population, but both are important and both are paramount.

Chagpar So, are clinical trials only an option if there are no other options?

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Fuchs In certain circumstances, some clinical trials are designed in a manner that if the patients have already exhausted the other standard of care approaches, that a clinical trial might be the best that particular clinical trial may be designed for patients who have already tried earlier therapies. But as well, many clinical trials increasingly now are moving novel agents into earlier lines of therapy, because what we are trying to do is add those therapies to existing therapies or alternatively the data from those agents is so extraordinarily promising that they really deserve to be part of the initial therapy. I think one clear example

that is emerging is immune-based approaches. So, as you know, there is an exciting emerging area of treatments that basically activate a patient's immune system to attack their own cancer. Yale is a world leader in this. Immunobiology at Yale is top notch and really has led the charge on this, and now there are series of drugs in routine clinical practice that are working for a variety of cancers. For many of those circumstances, those drugs were first tested in patients who had failed all other options. They had tried other drugs that were not working. But as we have now learned more about those drugs and their extraordinary efficacy in select populations, there are more and more studies saying "hey, you know what, let us start with these immune-based approaches" because it looks like they are better tolerated than our existing therapies for select patients and they are potentially more effective.

Chagpar This is Dr. Anees Chagpar and I am joined tonight by my guest, Dr. Charles Fuchs. We are talking about his new role here at Yale Cancer Center, and more importantly what I would really like to get from you in this next segment Charlie is your vision for where cancer is going. Every year in this country, more and more people are being diagnosed with cancer. They say that 1 out of every 2 American men and 1 out of every 3 American women is going to be afflicted by some sort of cancer in their lifetime. So, talk to me a little bit about where you see the field of cancer going in the future.

Fuchs I think it is a wonderful question, and I agree with you. In fact, this year about 1.7 million Americans will be diagnosed with cancer and the other critical statistic is it is estimated that now 39% of Americans will be diagnosed with cancer in their lifetime, because as we made great strides in the other major illnesses such as cardiovascular disease, the burden of cancer becomes more prominent. And it really is incumbent on us to figure out how to move this field and to create a vision to what we wanted it to be. And the initiatives of Biden and others I think have laid out a platform for us, but clearly at Yale, we want to focus on what are the important next steps realizing there is a variety of things that we want to invest in. We want to invest in the basic research, we want to recruit scientists focused on some of the key areas that we think will inform future cancer therapies, be it the genomics of cancer, the role of the immune system in cancer, the role of metabolism in cancer and as well think about other areas within the

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laboratory including prevention as well as early detection beyond developing novel therapies. We also want to ensure that we have the clinical capacity to care for patients. Our center is growing in its clinical volume, we want to make sure that we are accessible to patients not only across Connecticut, but across the region, and so we want to be recruiting our clinical programs with high quality people who are not only focused on exceptional compassionate clinical care but as well interested in science, who really want to be part of moving the field to the next level. There are certain other areas in between them that we want to focus on, because as I mentioned earlier, we want to be able to translate

bench science into the clinic and we want to make sure what we learn in the clinic is rapidly returned back to the laboratory so we can further inform it. So, how do we create that glue? We have to have resources that connect the two and what do I mean by that. I mean, an ability to make sure that when patients come to Smilow and Yale, that we collect their specimens, their tumor specimens for research, that we collect with their permission samples from them and then return those samples to the laboratory to make sure we understand the genomic characterization, what genes are driving that patient's cancer, and that I think is important not only because it informs the field but we increasingly know that it informs patient's therapy, so-called precision medicine that is delivering treatments that are based on the patient's tumor genetic outlook. But as well, we want to make sure that we create systems by which we can grow patient's tumors in the laboratory so we can study it in a dynamic fashion. We want to make sure that we have other resources that we can interrogate the patient's specimens in a way that can connect the clinic as well as the basic laboratory and also to make sure we have the resources in a capacity to do cutting-edge clinical trials so that we can offer our patients the best science that is going to ultimately improve their lives. We also want to make sure we focus on other areas. You know, cancer survivorship is a big issue. There are about 15 million people now who live in the US who are cancer survivors, and that is an area that has not been adequately studied. How do we ensure that their care is the best imaginable, that we focus on survivorship? We also want to make sure that we have resources that deal with the emotional demands on patients. So, as a comprehensive cancer center, I think there is a variety of things we want to do. We want to continue the great trajectory we are having in immunotherapy. This is really now the third rail of cancer therapy. The first three used to be surgery, radiation and chemotherapy. Well, immunotherapy is really now the fourth arm and Yale has become a leader in this area. We have great science, we want to figure out what are the next targets to activate the immune system into manipulating a patient's cancer. I mentioned precision medicine and we want to continue to focus on the genomic drivers, the genes that drive cancer, to leverage that information towards moving drugs into the clinic, and one thing we want to engage are the chemists because this is an untapped resource that many universities have not

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really taken full advantage of, namely fine universities like Yale and some of the others I have been affiliated with have extraordinary chemists and chemical biologists, and what we need to do is connect the discoveries we are making about the genes and work with the chemist to actually design drugs that target those genes that can then be our next generation of therapies. That is something historically that we have ceded to drug companies, right. We make the scientific discovery, we let the drug company develop the drug. Well, I think those days are sort of limited. Yes, we want to collaborate with industry and we have had great collaborations, we want to be able to do that on our own because I think we would be much more nimble, and what is wonderful about Yale is

the extraordinary talent in chemistry and chemical biology that I think will take these novel discoveries from the lab and move it into the clinic. And so, these are just some of the many things we want to do, be it in terms of novel treatments, bone marrow transplants, stem cell transplants, cell therapies, a variety of things that I could speak to and we want to basically embolden all of those arms at Yale and Smilow, like the other major cancer centers are similarly doing and work together to really improve the lives of the patients.

Chagpar I want to pick up on that last bit because one of the things that Vice President Biden said in the Cancer Moonshot and as he went around talking to leaders in cancer therapies is that so many cancer centers are siloed, you are all doing wonderful work, you all have great biologists and chemists and laboratory scientists and you all have great clinicians and you are all trying to do the translational dance between bench and bedside and you all are in silos and he wondered, and I think it is a good thought, whether in fact you can drive innovation by collaborating across institutions. Can you tell us a little bit about that and your vision in terms of whether you think that is feasible or whether you think that there are barriers that prevent large cancer centers from collaborating in a meaningful way?

Fuchs I think it is a combination of everything you just described. Let me just say that I think innovation is a function both of individual genius that is in part a laboratory scientist, clinician who follows what is a creative idea and moves it forward into what is going to be an important discovery that ultimately impacts patient lives. But it is also a function of collaboration. Because at the end of the day, you cannot advance these ideas without collaboration and that is what we do within Yale and Smilow as a comprehensive cancer center. It has been my privilege and in part I think the success of my own research programs has been beyond the independent observations we made, to collaborate not only across the university but also across major cancer centers. I have had the ability to lead global studies where we have taken a novel approach for stomach cancer and done some initial work on our own but then engaged

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other major centers across the globe to basically launch studies. For instance, we recently completed a study on an immune-based approach for stomach cancer. We enrolled that study across countries in Europe, Asia, North America, South America and ultimately got the study done 7 months earlier than we thought, and I think what we will have is high-quality data, and actually have information about how it works in many countries across the planet. So, it is a combination of collaboration as well as individual genius, but we cannot do it alone and I think the Vice President is correct. It really does require collaboration, and I actually was part of the working groups for the moonshot and one thing that was clear from our groups was that sharing data is critical, and that is actually one of the tenants of the moonshot is to create a database by which cancer centers can work together. Fortunately, Yale among others is a part of collaborative groups that are formed by the National Cancer Institute and we meet pretty

regularly. Oftentimes patients will ask me in my office when I am seeing patients and families, they all want to know, how do I find out beyond what is going on at Yale and Smilow, how do I know what is going on at the other major centers, and what I actually say to them quite sincerely is, I just came from a meeting in San Francisco where all the major centers represented, we are very forthcoming and we regularly share our data, and let me tell you beyond what goes on at Smilow and Yale, if I knew there was something that you should be traveling for, I would tell you and I have done that. So, I think there actually is real communication between the major cancer centers because we want to share our findings, because we realize that science is not about a one-off observation made at Yale or Harvard or some other fine institution, it has to be ultimately vetted across investigators and centers because if it is real, we all have to be convinced that the observation is valid. And so, you cannot do it alone and you cannot do clinical trials alone. The sense of collaboration that the Vice President has emphasized is actually happening and it is critical to our progress.

Chagpar You know, it is interesting we talk about global clinical trials, and I think the other key element that a lot of people do not realize is that more people die of cancer than AIDS, malaria and TB put together. And these three elements which have been part of the millennial development goals have been our focus for a long time. And yet, when you talk about immunotherapies and precision medicine, you wonder whether or not that is really translatable to low-to middle-income countries where people are still dying of cancers that should be preventable. Tell me a little bit more about your thoughts on the influence that major cancer centers in the US can have in reducing global cancer burden around the world.

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Fuchs I think it is vitally important and I would even take that one step further. You are absolutely right, access to these treatments, fundamental treatments for cancer in parts of the world that do not have access to it, it is incumbent on us to make sure that access to care is adequately addressed in the US because let us be clear, it is not perfect and one thing we are committed to as the cancer center for Connecticut and for the region is to ensure that our fundamental discoveries and findings and access to excellence at Yale and Smilow is available across the region because I do not think that is routinely available and we want to make sure and there are clear studies showing that access to care is critical to improving patient's outcome, in part explains differential outcomes and disparities that is for lower socioeconomic groups, for minorities that access to care is a driver for why their cancer outcomes are worse. And it is clear that if you eliminate those differences, you can actually improve the outcome. We have to do the same thing globally, and that is a commitment that we are making at Yale.

Chagpar Dr. Fuchs, I could sit here and tap your brain for the next hour, but sadly we are out of time. It was so great having you as my guest here on Yale Cancer Answers. It has been a terrific show, getting to know you and your new

role. Until next week, this is Dr. Anees Chagpar wishing everyone a happy and healthy week.