

# Yale CANCER CENTER *answers*

WNPR Connecticut Public Radio



## *Hosts*

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Associate Professor of  
Surgical Oncology

### **Francine Foss MD**

Professor of Medical  
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## Translational Medicine

### **Guest Expert:**

### **Theresa LaVallee, PhD**

*Vice President, Translational Medicine,  
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## **Yale Cancer Center Answers**

is a weekly broadcast on

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*Welcome to Yale Cancer Center Answers with doctors Francine Foss and Anees Chagpar. Dr. Foss is a Professor of Medical Oncology and Dermatology, specializing in the treatment of lymphomas. Dr. Chagpar is Associate Professor of Surgical Oncology and Director of the Breast Center at Smilow Cancer Hospital at Yale-New Haven. If you would like to join the conversation, you can contact the doctors directly. The address is [canceranswers@yale.edu](mailto:canceranswers@yale.edu) and the phone number is 1-888-234-4YCC. This week, Dr. Chagpar is joined by Dr. Theresa LaVallee for a conversation about translational research. Dr. LaVallee is Vice President of Translational Medicine at Kolltan Pharmaceuticals. Here is Anees Chagpar.*

Chagpar Theresa, let's start off by having you tell us a little bit about yourself and what you do?

LaVallee Sure, I am a PhD in biologic sciences and I have spent my career working in drug development and trying to use science to bring drugs to patients that are more effective.

Chagpar How exactly does that happen? I think that all of us who have ever been treated by a doctor who gives us a drug must at some point wonder how the heck this happened. Can you walk us through that whole sequence that finally gets you the medicine at the drug store?

LaVallee It is clearly a long process and it is a science-driven process that starts from early laboratory work where you are identifying different ways of looking at what is driving a disease, so if you think about a car and having it go, what is the accelerator, and in terms of cancer that cell has essentially turned off the brake mechanism and so the idea of the drug is to come in and put the brakes on and hopefully destroy the cell and so having a good understanding in the laboratory about what is pushing the accelerator on and then trying to match either a chemical or an antibody based drug to put the brakes on, and then as you go through development it is early in the laboratory to really look at both the activity of the drug, does it truly stop a cell from growing in the case of cancer? And then also the safety, because it is clearly equally important that you do not have unwanted or too many side effects in a patient and then you go through early clinical development. Model systems have limits, like all models do, and so testing it in people in early clinical trials to get a handle on the dose and the safety and then testing it against other marketed drugs to show that you deserve a space in the market, because clearly you do not want to bring an inferior product to the patients.

Chagpar In that whole process, it seems like there would be a lot of difficult steps. In your mind, what is the hardest part of getting a drug to patients?

LaVallee That is a difficult question because it is such an integrated process. The understanding of what the models are telling you and understanding how best to treat is the hardest part I think looking at it from my perspective as a translational medicine person, I am sure if you are asking someone who is involved more in manufacturing they would talk about all the complexities of actually making a drug in enough scale to bring it to a person, but I think the thing that we are just starting to is

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understanding which patients to treat as we try to select people that are suited for the treatment. Disease have a lot of heterogeneity to them so lung cancer is not a single disease and trying to figure out what the features are to select those patients in lung cancer or breast cancer or whatever it is, that is best suited for your treatment.

Chagpar The other thing that I thought of as you were explaining the whole process, that would be difficult is at the fundamental levels, the whole thing rests on figuring out what is pushing on the accelerator and what could push on the brake. How do people figure that out?

LaVallee Again it is through both studying model systems in the lab as well as I think studying patient samples and looking and setting up clinical studies to answer those questions. In cancer, we have tools where we can grow cancer cells in a test tube and look to see if we can turn the growth off so that they stop growing in the dish and then we can put them in mice where we look at the growth of a tumor in a mouse and if we treat that animal can we remove that tumor? And then of course those systems are much more simple than going into something as complex as a human, but the thing that translational medicine is really bringing to the field is that we are turning clinical studies into science driven studies, so that we ask whether or not that is a driver or an accelerator and I think an example of that to make it understandable as is a drug called crizotinib that was recently approved as a drug for lung cancer and so in the lab people felt that a protein called MET was the driver and they had lots of really beautiful data in the test tubes and in the mice to show that was true and then when they put it in humans with lung cancer and looked, the patients who did the best weren't necessarily the MET expressers, but the ALK expressers and that is a small subset of lung cancer patients, less than 10% and so you can test it without screening for that ALK driver and now it is a marketed drug that is affording a lot of benefit to patients and so that shows you as we take it from the lab with an idea that MET was the answer, but in the clinic we found in humans that ALK was the answer, so it is still a therapy that is effective, but it was only because they asked the question in the clinic.

Chagpar Another thing that seems important in what you just said is that there may be more than one thing pushing on an accelerator and more than one thing that could push on the brake and it may be trying to figure out in a given patient, in a given tumor, which is which?

LaVallee Particularly in cancer I think that is true and it is rare that you have a single drug that can answer things for patients and that is why we have combination treatments and figuring out which drugs go well together both from a safety perspective but also that they both turn off the accelerator and not one turned it off and one turned it on so it is complicated in that sense, but again as we keep asking questions and as we are developing things, we understand it better and are doing a better job of bringing effective therapies to patients.

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- Chagpar The other question that I think a lot of patients have is, we often talk about finding the answer to ‘cancer’ across the board. Are the accelerator pedals and the brake pedals for different kinds of cancer the same, or are they different?
- LaVallee And the answer is yes and no. As we are looking more and more today at developing targeted therapies, and so in the example that I gave with the MET which is now there are MET inhibitors that are coming to late stage clinical studies and really showing activity and asking across different tumor types that are MET expressing tumors, are they active, not is this a lung cancer drug, is this is a gastric cancer drug, but this is a MET drug and where is MET present and then another example of where it can be similar across different tumor types might be the immunotherapies which are really having a phenomenal effect in revolutionizing cancer care. I think there are expectations for what an effective therapy is, again with the brakes and accelerators example, the immune system has turned off our bodies mechanisms to get rid of the cancer and made our immune cells, our T cells which can kill the tumor cell, quiet and essentially asleep so the brakes are on and there are recent drugs against proteins like CTLA4, PD-1, PD-L1 that essentially take the brakes off and allow the T cells to wake up and kill the cancer. And that is particularly important because then your immune system, if the cancer comes back, will clear it. So the long term survival is being seen and it is being seen across a very broad range of tumors and they are just now trying to understand if this is against essentially people with cancer, or is it a subset of people? Or is it that particular tumor types are sensitive? So the complexity with cancer when we talk about it is that it is really 900 different diseases and so depending upon the therapy, it can work broadly across different cancers or may be more focused to a particular cancer type. Even in breast cancer, clearly if you are going to target the estrogen receptor that is going to be more focused towards breast cancer versus other tumor types.
- Chagpar The interesting thing with immunotherapies that you brought up, that I think is so exciting is now we can rev-up the immune system, because your immune system, much like it fights off a cold or whatever else and gets rid of the virus or the cold, it could potentially get rid of cancer. One question that I think people may be asking and certainly is a question of mine, is anybody looking at revving up the immune system to stop the cancer from getting there to begin with?
- LaVallee There are vaccines, and clearly we have a vaccine now for cervical cancer and people have spent decades trying to get it to be broader and I think it goes back to your initial question, that there seems to be an on/off a lot like accelerators and brakes, so how do you get a vaccine that is broad enough to be able to take into account all those different approaches? I think with time, we will find incremental benefit for where it can sometimes be the answer, but it is not going to be the answer for all.

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Chagpar Tell us a little bit more about how you interface, you work at a pharmaceutical company, how do pharmaceutical companies interface with academia and with clinicians, how does that whole process work?

Lavallee This is a great question. Recently I participated in a Career Day at a University and was asked how do you decide between academics and industry and my advice to people in science was follow your passion. Figure out what you want to do and then figure out where best you can do it and I do not know that there is a large distinction per se, because we cannot do our jobs successfully in a company setting without strong collaboration and I think that is a key success factor, working with academics is really important, and with clinicians.

Chagpar Theresa, I want to pick up on how you made that choice and what the passion is that drives people in pharmaceuticals versus in academia? We are going to do that right after we take a very short break for a medical minute. Please stay tuned to learn more information about translational research.

*Medical Minute*

*It is estimated that nearly 200,000 men in the US will be diagnosed with prostate cancer this year and one in six American men will develop prostate cancer in the course of his lifetime. Major advances in the detection and treatment of prostate cancer have dramatically decreased the number of men who die from the disease. Screening for prostate cancer can be performed quickly and easily in a physician's office using two simple tests, a physical exam and a blood test. With screening, early detection and a healthy lifestyle, prostate cancer can be defeated. Clinical trials are currently underway at federally designated comprehensive cancer centers like the one at Yale to test innovative new treatments for prostate cancer. The da Vinci Robotic Surgical System is an option available for patients at Yale that uses three dimensional imaging to enable the surgeon to perform a prostatectomy without the need for a large incision. This has been a medical minute and more information is available at [yalecancercenter.org](http://yalecancercenter.org). You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.*

Chagpar Welcome back to Yale Cancer Center Answers. This is Dr. Anees Chagpar, and I am joined today by my guest, Dr. Theresa LaVallee and we are discussing Translational Research. Theresa, right before the break we were talking about your decision to go into industry and that at a recent career fair you told science students to follow their passion and I loved that because that is what I tell all of my students as well. Tell me what it was about industry, about Pharma that attracted you as opposed to academe?

LaVallee From a very early age I was always interested in science, particularly with an application to medicine and even initially considered whether to go into a medical profession or research and found that what really interested me was what made people sick versus the direct patient care. From that aspect, what I have always looked for are ways to still have an impact on patients and

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for me, industry gave that opportunity because research is such a fundamental part of that and being able to work on studying diseases and ways to attack the diseases with the idea of getting medicines to patients. As you go through and do clinical studies and see those tumors shrink in patients, that is a very exciting moment and I think that is what my passion was, to really be able to say, we did work on a disease and were able to develop a medicine that helps someone.

Chagpar Can you do that in academia too? What is the difference? Or are they very similar?

LaVallee They are integrated in so many ways, you need that collaboration and clearly in an academic environment they have a huge contribution to doing that. The actual complexity of developing a drug in the number of departments and the amount of money it takes to really bring it forward makes it difficult in an academic setting, but it has been done. There are clearly investigators that have discovered drugs and brought them to the clinic on their own, but to do it in a broad sense, it is much easier to do it in an industrial setting and you still have the opportunity to do collaborations with a number of academics. I am currently employed at Kollten Pharmaceuticals, which is based at Yale Medical School, and there is a very strong collaboration and that was one of the things that attracted me to that position, having such talent at Yale and the ability to collaborate with so many scientists to hopefully, between the collaboration and the partnership, be able to develop our drugs better.

Chagpar I think it is a beautiful marriage. You are a PhD in your own right, do you still do the bench laboratory research or are you more collaborating with other researchers who are doing that initial finding of what is the brake, what is the accelerator and then taking it from there to move it into drug development?

LaVallee It is both. We have lab capabilities. It has been a while since I have done lab work myself, unfortunately in some ways, but we have a group of very talented scientists at Kolltan in the lab that are doing research activities and then in partnership with various academics have collaborations that are really much more geared towards specific questions or maybe they have a technology that we do not have or a particular focus in a disease and another aspect of drug development that I found incredibly successful is if you can position where you do a collaboration both in the lab and in the clinic with people you would like to do your clinical trials with because the physicians know best what their patient's needs are and what is effective and having their input and their scientific contribution on how you are developing it and how to position it before you treat their patients makes a much better marriage and stronger data packages to get these drugs through.

Chagpar Let's go back to the whole process of drug development, and this is something that I think is really pertinent when we think about not just drugs, but anything, technologies and other things that we are trying to get from an idea from the science, from the basics, to actually having something

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physically able to help other people and I cannot imagine how that would work without an industrial partner who can figure out all of the regulations and things that a drug process needs to go through in order to finally get FDA approval. Can you talk a little bit about that process?

LaVallee From a drug development perspective, if we think about it once it enters the clinic, so we will start there, to do that you need to submit a package to the FDA if you are doing studies in the United States, and clearly the FDA's real focus and mission is the safety and welfare of the people and so they are looking for both safety and efficacy, particularly in cancer because taking a person who is very sick and giving him treatment that has no chance of helping is also a cost to them, but then from a clinical perspective, once you get that agreement with the FDA for phase I clinical development it is about starting with low doses to really understand the safety in a human because this is the first time you are treating a human, you want to see what the effects are on the body systems and how it metabolizes that drug, how the person is taking it, and particularly in diseased patients, they might have different processes and systems that are working differently. So in phase I we really look for safety and biologic effects in setting our dose. The dose is really important and if you are lucky that will take a year and then you go into what we call phase II which is a refined dose or doses one or two doses in a defined patient population so not just cancer patients but head and neck cancer patients, or breast cancer patient, and you treat them either as with your drug alone or in combination with another drug and look for activity read. So really saying, do you have enough activity to invest and then a phase III study which includes hundreds of patients because to register a drug with the FDA you both have to show safety and efficacy, risk-benefit as we often hear the FDA talk about, and for that you need a couple hundred patients and in fact the FDA requires 300 to 600 patients in your safety data base. So that is a lot of time to do all these clinical studies with all of these people and you need a large amount of drug and that is probably why it is more well suited for an industrial partner to do this because the cost of manufacturing and the clinical trials is quite large.

Chagpar All of this is being done before you have FDA approval. So I can imagine that process takes a long time.

LaVallee It does, that can take years and I think the focus of translational medicine is to learn early because clearly a phase I clinical study is fairly short and if you only advance compounds with a higher likelihood of succeeding, then you do not take as much time in many but the other thing is treating the right patient. When we talked about the example of crizotinib, which is an ALK inhibitor. If it is present in less than 10% of lung cancer patients, if you did a study with a hundred patients and did not actually ask for the patients to have that ALK, you may not get a signal whereas if you just screen for that marker and then treat those patients, it is a much smaller study and so I think people are very interested in translational medicine to try to get a better activity read but also in a shorter time frame.

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- Chagpar How long does it usually take to get a drug from phase I to actually routine FDA approved, ready to use off the shelf?
- LaVallee Clearly, there is no one answer and it really depends upon what the disease is. So in cancer there are different cancers and usually you will see a first approval in later stage disease which essentially means that the people are pretty sick and so their life expectancy, because survival is the endpoint, is relatively short and so it would take a couple of handfulls of years, so 5 to 10 years would be the norm but we are seeing with some of these agents such as some of the immunotherapies now that are really coming up the PD-1 and PD-L1 where they are going from phase I to phase III because they are seeing such good reads early and other compounds that are going into phase I and selecting the patients upfront and then go directly into the phase III. So the crizotinib story was only a couple of years. There is a broad range, but when you do an average it is a couple of handfulls of years.
- Chagpar I can just imagine that there are people who are listening to us who are thinking, you know we want to find therapies for cancer, in particular, that are safe and that are effective, but it is not good if it is just an idea that is sitting on the shelf. We need to get this into the hands of patients and anything we can do to accelerate that process will certainly help. Tell us a little bit more about where you think the future of cancer research is going and how we get there?
- LaVallee We have made amazing strides over the last few years and it is hard to say what has been the largest success factor, there are probably several different answers to that question, but the answer that I would give is the understanding of who to treat. Even when we think about leukemias and lymphomas, so the blood cell based diseases, in the 1960s and 1970s they were basically just called leukemia or lymphoma, and now we have so many different subsets of that and we are really seeing remarkable benefits in those patients, so instead of just a lymphoma, there are hundreds of lymphomas and trying to match the treatment to go with the patient. A recognition that the cancer is heterogeneous and that you have to define that subset of people that are best suited for your treatment even with the immunotherapies. I think the CTLA-4 benefit is tremendous but it is in 10% of patients. So how do you select those 10% upfront to get that remarkable survival? PD-L1 and PD-1 seems to be more like a third or maybe a half, the data is still evolving but it is not everybody, so there is no one answer in finding that and I think that it is an exciting time because it gets people treatments that are apt to benefit and does not waste their time with toxicities and treatments that are not going to help.
- Chagpar Is genomics part of personalized medicine?
- LaVallee That is an interesting point. I think that genomics is a part of it but it is only an answer and one of the things you really have to be careful about is asking for a single technology to give us all the answers.

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