

Yale CANCER CENTER *answers*

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Translational Research and Lung Cancer

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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 and the phone number is 1-888-234-4YCC. This week, in observation of lung cancer awareness month, Dr. Foss welcomes Dr. Roy Herbst and Dr. Julie Boyer. Dr. Herbst is Professor of Medical Oncology and of Pharmacology, Chief of Medical Oncology at Smilow Cancer Hospital and Associate Director for Translational Research at Yale Cancer Center. Julie Boyer is Associate Director for Translational Research Administration. Here is Francine Foss.

Foss Given that November is Lung Cancer Awareness Month, Roy perhaps you could start out the show by talking a little bit about how common lung cancer is and how we are doing as far as treating lung cancer.

Herbst Sure, thanks for inviting us. Lung cancer, unfortunately, is the number one cause of cancer death both in the United States and worldwide. In the US there will be almost 200,000 deaths due to lung cancer this year and worldwide, some places close to 2 million deaths. It is a tremendous medical problem. It is not the number one cancer diagnosed. Breast cancer is more common by incidence, in large part because we screen with mammogram, and prostate cancer in men because we screen with PSA. We are just beginning to start to screen people for lung cancer but unfortunately that still has not paid dividends in current practice though that will be happening very soon.

Foss Roy, we talk a lot about smoking as being the obvious risk factor, but I understand that the incidence of lung cancer is increasing in nonsmokers, are there other risk factors that have been identified? Can you talk a little bit about that?

Herbst If you look at what the causes are of lung cancer, of course at the top of the list is smoking and then such things as asbestos and radon gas, whether you live in the city or the country. As many as 80% of patients have either smoked or had a close history of smoking in a family member or in work environment, for example, flight attendants before smoking was stopped on air planes. About 20% of patients with lung cancer are people who have not smoked or smoked very little. I am not so sure that this is increasing, I think it is just that it has been noticed more, and identified in the last five to ten years and it is important for a number of reasons, most especially that there is specific genetic alterations that result in the lung cancer in these patients who have never smoked and that can result in treating them in very specific ways that can be more effective and less toxic. For example, some patients with never smoking lung cancer might have mutations in the epidermal growth factor gene and this means that their cancer is growing based on an engine that is driven by a certain factor, and we actually have oral agents, drugs that can treat these patients as well and

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that is true for a couple of other subtypes. So it is important when someone comes in that we take that history because it can help us guide the therapy.

- Foss You touched on an important point and the subject of our show today, which is talking about translational research in the context of lung cancer. You and Julie work together on translational research. Would you tell our audience what translational research is and how the two of you interact?
- Herbst Absolutely, Dr. Boyer and I work very closely here at Yale Cancer Center to develop translational research. The Yale School of Medicine and Yale Cancer Center have always been quite strong in clinical practice. It has also been quite strong in basic science. The first chemotherapy drugs were developed here at Yale School of Medicine in 1942 by Dr. Goodman and Dr. Gilman, that being nitrogen mustard during World War II that was given to patients, but the key thing now is to take that basic science and bring it to the clinic so that these great discoveries can have an impact on patients with cancer and how to deal with shrinking their tumors and with side effects. What we do in the office of translational research at the Cancer Center is try to bring the scientists in the labs together with the clinicians who are working with the patients and bridge that gap so that we can more quickly bring more effective therapies to the clinic.
- Boyer That is right, and we are doing that very effectively for lung cancer. Right now there is a very strong translational working group of physicians and basic scientists and population scientists and we are really trying to stimulate these types of working groups in other disease areas, in breast and myeloma and glioblastoma and we have done that through several initiatives through our office. We want to encourage joint seminar programs. We want to encourage joint grant applications so that these working groups have a real solid foundation to continue working together.
- Foss Julie, you are head of the translational research program overall for Yale Cancer Center. Can you talk about how you actually bring those groups of people together?
- Boyer Certainly, we try to do a number of things, as I mentioned we try to encourage joint seminar programs. We have instituted a pilot grant program where we encourage groups of investigators to work together, particularly with a biostatistician from our biostatistics department, and these working groups need to be composed of both basic and clinical scientists, and the intent it to provide a little funding to get these research programs nucleated with the hope that eventually they lead to external grant funding and we have been very successful in that for this year. We gave four such awards to members of the Cancer Center and 4/4 of those recipients have gone on to either have plans for applying for external grants or have already applied for something like that.

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- Foss That is a terrific statistic for the audience. You are specifically referring to the fact that those researchers were able to develop their programs here at Yale and then get funding, say by the federal government, by the NIH?
- Boyer That is correct. It is pretty new, we just gave them the first round of internal funding at the beginning of this year and we do not know exactly what the external funding will translate into in dollar amounts because it takes a while to learn from the government whether or not your application will be funded, but we anticipate given the strength of programs that they will be very successful.
- Foss You are a clinician, you are a doctor that actually sees patients, but you are also a researcher on the other end. Can you tell our audience how important the research that is going on in those basic science labs is and how that actually gets translated into the clinic? How does that impact what you do for patients?
- Herbst It has a huge impact on patient care and for those who might be listening who either have cancer or know someone with cancer, right now with all that we know in the last sixty years since the discovery of DNA and then RNA, and proteins and how cells grow, now when we see someone with cancer we have to and want to treat them in a more personalized way. You do not just want to take drug A or drug B and give it to all patients with lung cancer, colon cancer, or breast cancer. We can do that in some cases, but what we really want to do is dissect that, and figure out what is it specifically about someone's tumor that is causing it to grow? What is the gas that is causing that car to move at 60 miles an hour? We want to inhibit it and stop it so that we can target the therapy, and what Julie is talking about with all these initiatives, they are all very important here at Yale because it is serving a number of very important goals. The first goal is that when someone comes here we want them to have the best therapy they can get for their cancer, whether it be lung cancer as we are talking about today, or any other type of cancer that they might have and we do that by when they first come to visit we take a piece of their tumor and we profile it in our pathology labs. We can actually look at 60 to 70 different genes and we can create a profile so that we know a little bit more about their cancer than we knew when they first came to see us. And then what we are doing, and this is where the translation comes in, is we are matching that genetic profile, we are matching that characterization of the tumor with drugs, either a single drug or a combination of drugs that can really help that patient more effectively and with less toxicity, and as you heard, we have to do that with programs. We need research because the research is impacting patients in real time. Very often when someone comes in we might have a clinical trial and that clinical trial might be for a very specific type of lung cancer and we could use the information from that profiling to put someone on a much more specific therapy. We are very excited about this and the fact that we can both improve clinical care, which is the number one goal, while also discovering new ways of treating patients with lung cancer, the second goal,

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and doing it altogether and creating a team, a multimodality team of surgeons, medical oncologists, radiation oncologist, nurses, nurse practitioners, and social workers. It really is just wonderful. I have only been here at Smilow about a year and a half, but certainly I have seen things grow enormously in that time and before that with Dr. Lynch as the Cancer Center Director and the rest of the team. We really are in a great period of discovery and improved patient care here at Yale.

Foss And Roy, just for the audience, you came to us from MD Anderson Cancer Center in Texas, welcome to Connecticut.

Herbst Thanks, I actually went to college here a number of years back, so it is good to be back.

Foss So, you have ties here?

Herbst Yes, I have ties, I could live without some of the winters, but it will be okay.

Foss Can you go back to what you had just talked about, which is that now we are actually taking pieces of tumors and looking at the genes, how easy is it to do that? If a patient say has their initial biopsy or surgery at another hospital, is it possible for us to get a hold of that tissue? Do we need to get fresh tissue and do we have tissue banks now with these samples?

Herbst The answer is yes to all questions. Let's take them one at a time. If someone had their initial diagnosis elsewhere, which many will, and want to come here to our lung clinic for a second opinion and perhaps they enroll in one of our clinical trials, we will try to obtain the initial biopsy. Normally that has been preserved in paraffin, a waxy type substance, and hopefully there will be enough tissue that we can then do some of this profiling work, some of these genetic studies here at Yale. So that is being done. In some cases, either because the initial biopsy was not adequate, or we need more tissue because we are doing a special study, for example we have a trial that I lead and Dr. Boyer is working very closely with me on this, known as the BATTLE trial, which is a biomarker assisted targeted therapy for lung cancer where everyone gets a fresh biopsy because even if they have had a biopsy before, we realize that these patients might have had other therapy since that first biopsy and tumor cells, unfortunately, are very smart. The tumors cells that are left in that patient are not going to be the ones that were there six months ago, they are the ones that were resistant to all the therapies that that patient has had. So in that case we might want a new biopsy, but that is good because if we can get that new biopsy and we do that on the clinical trial and we have some research support to help this study, we can then get this new biopsy, we can analyze the results from that biopsy in about a week and a half or two weeks and then use that result to then put the patient on one of three or four different therapies more specifically targeted for their tumor. The third thing is that we have a very large tumor bank, and actually when I was a student here at Yale many years ago we used to go to the movies around Exit 41 off I-95, there was a big Showcase Cinemas there, and of course that became the Bayer facility and now it is Yale's

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West Campus. And that is an enormous resource. Can you imagine, that facility has laboratories, it has a DNA sequencing facility that is one of the best in the country, so we can actually go from head to toe and look at every aspect of this tumor to try to find something to use in real time for the patient who comes to see us, and also learning from our experience, from our tumor bank, we can help many patients. Julie and I have been working on obtaining samples from a large number of different places to analyze as well.

Foss That is great, and I would like to talk more about the BATTLE trial in a few minutes when we come back from our break for a medical minute. Stay tuned to hear more information about translational research from Dr. Roy Herbst and Dr. Julie Boyer.

*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. More information is available at yalecancercenter.org. You are listening to the WNPR Health Forum on the Connecticut Public Broadcast Network.

Foss Welcome back to Yale Cancer Center Answers. This is Dr. Francine Foss and I am joined today by my guests Dr. Roy Herbst and Dr. Julie Boyer and we are discussing translational research. Before the break, Roy you brought up the BATTLE trial and you talked a little bit about this as a groundbreaking approach to treating lung cancer, and I was particularly intrigued when you said that within two weeks you could get all the information you need to decide how to treat a patient. For the audience, how groundbreaking and innovative is this trial and this concept that within two weeks which is the time it sometimes takes to get a CAT scan, you can give us specific information about these tumors that is going to direct therapy? How big of an impact does that have?

Herbst I think it has a big impact. It is actually a program that my colleagues and I first developed when I was in Houston at MD Anderson back in 2005. At that time it was unheard of that you might ask someone who already has been treated for lung cancer, already had a biopsy, come in to see you to get a new biopsy, because remember, you have to think about the patient who is undergoing this procedure, the cost, the time, and then to use that biopsy to put the patient on one of three or four different treatment options. We did this back in Houston and it was quite successful and it really

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did help to change the paradigm in this disease. And it did hurt that during this period we learned that especially in the people who had never smoked, that certain gene mutations can result in information that can allow for more effective therapy. So it became the mantra that you have to have some tissue in someone with lung cancer. From the initial BATTLE program at MD Anderson about a year before I left, we developed a program called the BATTLE II which is the new BATTLE program, so when I came to Yale, it was my goal from the very beginning to bring that program here as well. Dr. Boyer helped me to do that. We are doing this program in collaboration with our colleagues at MD Anderson, which is wonderful because if we are going to make an impact against this terrible foe cancer, I think large centers, top centers like ourselves need to work together. So, it is a large MD Anderson of Texas and Yale-New Haven collaboration, but we are able to see these patients, the trial is up and running. This is a team approach. We have Dr. Eric Reiner who does most of our CT-guided biopsies. We have Zenta Walther and Jeff Sklar, our pathologists, who in real time are processing these samples, some of the work is done here in New Haven, and some goes over to Houston. We have Emily Duffield, who is a tremendous research nurse practitioner who works with us on this program along with Brie Hamel, our project manager and the list goes on. It is a team approach. The thing that has been so wonderful to see is one of these programs in place, and it is good for the patient, which is always our number one goal. We are also learning a tremendous amount because not only are we figuring out how to treat these patients, but we are focused on very hard to treat types of lung cancers including some that are driven by a gene known as KRAS which is a horrible mutation to have in this disease, and we are able to try to figure out new therapies for that and then what we are able to do is we are able to export this program not only to lung cancer, but what Dr. Boyer and I are doing through our office of translational research is trying to make this a reality in the breast cancer program and then the gastrointestinal cancer program and some of the hematologic malignancies, the lymphomas, the leukemias, where I know you work. This is really something that is changing the way we practice here at Yale, all the components are in place, and as you are well aware the Yale network is expanding because we brought in practices from around the state. So, if you are seen in Hamden or in Waterbury, at one of our Yale Facilities, you can enroll in this type of program as well, because they can have the whole process done, so we have really expanded the range. We give better options for patients and in the meantime we continually focus on our research. This program is funded by the National Cancer Institute by a peer reviewed grant so the government thinks enough of it that they are supporting it as well. We really are very proud that we have this in place for our patients and I am just thrilled by the team that we put together and how well people are working together and I am not surprised, but teams do take time to build and it is nice to see this is in place.

Foss Julie, you have been involved with this from the very beginning, can you talk about what Dr. Herbst eluded to, how difficult it is going to be to export this to some of the other disease groups because I am sure a lot of people in the audience are thinking about their cancer and whether we are ready to profile their tumors?

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- Boyer I think that the example of bringing the trial to Yale from Houston and opening it here is a great example and it shows that it definitely can be done and I think that it will not be so difficult to transport it into different disease areas. We know now that the infrastructures are in place, we know that we can handle the sample collection and processing and it's a really fabulous trial and like Roy said, not only does it help the patients get the very best care that they can, but it also is a great example of the translational research continuum and at a place like Yale where we are trying to stimulate this type of work and more trials like BATTLE, not only do we direct patients to the best care for their cancer, but we also learn from all of the samples that we collect, we learn at the molecular level what is going on and what we can do for the next phase of trials or the next stages of drug development, and we learn from the responses these patients have to these drugs.
- Foss In terms of the translational research component of this, can you talk a little bit about how that information is disseminated on the campus, say to some of the other scientists in different areas of the institution that may not be working on lung cancer now, but might be interested in some of these genes? Is there a mechanism within the institution or even between Yale and other institutions to disseminate what we are learning here?
- Boyer Yes, to start with we have a large team working with us so the data is readily available and we spend a lot of time talking about the BATTLE trial and the results and we encourage lots of collaborative activity with our group. Roy, do you have any thoughts on this?
- Herbst We wear many hats, and the other is with Karen Anderson in the Developmental Therapeutics Program here and one of the ideas is to build developmental therapeutics, which is new drug development at Yale and to build it in a personalized way. We have had retreats and we have had seminars where we talk about this approach. We also recruited, just in the last three months, Dr. Paul Eder. He had previously been at AstraZeneca Pharmaceutical, but before that he led the phase I unit at Dana Farber/Harvard for many years. We now have fertile ground where we have someone who is bringing in new drugs against new targets and then we have the BATTLE approach in lung. We have the pathology group with Dr. Sklar and Dr. Walther who are doing this for all tumor types and then of course Dr. Richard Lifton and the work that he does in the DNA sequencing facility here at Yale. So, we really have all the pieces in place to take this approach to any type of tumor and the one thing that we have been very focused on in the lung group is re-biopsies. So, someone comes in, they fail the protocol, we get this new biopsy, we put them on the BATTLE, but they might fail the BATTLE too, and then we would get another biopsy and then figure out what to do next and that's really the important thing that we are able to do that. We can figure out what to do next based on what the tumor is telling us, but the problem is that we do not always know what the tumor is telling us because this is such a new area, and that is where the research comes in and that is where we are working in lung cancer, but similar things are going on in breast cancer and colon cancer and other tumor types and it might be that similar mechanisms are in play and it is not where the tumor is coming from, but what is causing the tumor to grow and so we are really looking at cancer here in a very different, more precise way, focusing on the genes

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and the proteins. We are at the very early stages of this, but it has been wonderful to see it grow, and we are expanding. We are bringing in more physicians as you know and more people to do the clinical trials and the clinical research. Yale really is a place where we are seeing patients come from far away, people are coming from around the country now for some of these trials and that is very good to see.

Foss People are hearing the news, the news is out as to what is going on here and you are getting referrals coming in from all over?

Herbst Right, we participate in national meetings and forums, we are publishing papers and articles, and it has always been known that the basic science here is second to none. There are few medical schools that have the amount of discovery as Yale, but I think what is emerging are more and more reports of clinical studies based on this emerging science that are really having wonderful input into how patients are treated and we are collaborating as well with groups around the country but I do feel like we are back on the map as a novel therapy center for cancer, lung cancer and other tumor types and that is only going to grow in the years to come.

Foss I just wanted to touch on the clinical trial issue that you brought up as well. Can you talk about the interface between these translational programs and the actual clinical trials that are going on at Smilow Cancer Hospital?

Herbst One of the things that Julie and I work hard to do is we want to develop clinical trials within disease programs so that they are not empiric, if someone comes to us at Yale and says, do you want to run our clinical trial, we may or may not do it but what we are more interested in is trials that are based on the science and what we have discovered in the lab and from working with some of these clinical specimens. If we discover, for example, in lung cancer that 25% of patients with lung cancer who are not doing well with the conventional therapies, have a mutation in their gene known as KRAS, then we want to figure out how to target that abnormality and develop trials in that area. Then we will look either within our own development here, we have chemists here at Yale who are developing compounds and we meet with them once a month to try to see what they are doing and how we can link that. It is a very nice meeting because it brings together the most basic of scientists with the clinical of clinicians, but these are the types of things that are going to raise the bar, that are going to help us make inroads into this disease and that is something we work hard on.

Foss Are you also working with pharmaceutical companies that are developing some of these novel compounds and are there partnerships that have been developed between your group and some of the drug companies?

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- Herbst Absolutely, at an institution like Yale you can only develop a few drugs totally in house, we have some companies here in town, but we also work with some of the major pharmaceutical companies and actually that is one of the things Dr. Boyer have been very involved in and trying to make these partnerships a reality.
- Boyer Absolutely and we have effectively partnered to test some of these compounds from different pharmaceutical companies in the earlier stages of clinical trials and that has only grown since Dr. Eder has joined us and we hope to do much more of that.
- Foss What that basically means for the audience is that there might be a brand new drug that nobody else can get that you might actually be able to get through a study that is being run here or at another Cancer Center?
- Herbst Francine, I was always impressed over the year as I watched Yale from down south and what you are doing in T-cell lymphomas and I know people come to see you from many different places because of the clinical trials and the biology and the understanding you have of that disease. Now in the solid tumor malignancies, and in lung cancer ,today's subject, we are trying to have a portfolio of studies of drugs that target these abnormalities, because if someone comes to see me and I say okay lets get a new biopsy, let's profile your tumor for the 60 or 70 genes, or maybe even sequence the entire tumor, that is all well and good, but then when I see that man or woman in the office a week later, they are going to want me to say, okay we have this information here's what we are going to do." And in order for me to do that I need to have a panel of different drugs, hopefully the newest drugs and the newest combinations, rationally developed and brought to Yale that are being tested for safety and efficacy that I can then use to match the patient. So, we are trying to create that that sort of environment and that sort of program, in some cases if we do not have the right thing here we can partner with colleagues and we are part of cooperative groups around the country. There are networks and we are very active in that realm as well. But that is the goal, to be a place someone can come to with that very difficult to treat tumor that has already grown despite conventional therapy and we can figure out what to do that might be a little bit better, or hopefully a lot better than what they are getting, and that is the challenge and that is what really keeps us and our team focused and working both in clinical care and research.
- Foss We just have one minute left, but I wonder if you could give us some hope for the future for patients with lung cancer?
- Herbst Clearly in the 20 years I have been doing this we have seen this field change dramatically. When I was a fellow metastatic lung cancer, meaning the disease had already spread from the lung, was very difficult to treat, and in that situation we would give chemotherapy, and now about 20% to 25% of patients, because of this DNA tumor profiling, where you take the tumor and test it, have some sort of abnormality that allows them to get a therapy that is much less toxic than chemotherapy and much more effective, for example we talked earlier about the epidermal growth

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factor receptor, that is about 10% of the patients and there is something called ALK, that is another 5% or 6% of patients. There are a few others known as ROSS and so forth, I will not go into all the details, but now in about 20% to 25% of patients we can give a specific therapy and in almost all cases it is oral, it is a pill, so someone goes home with a pill and it will not work forever, but it can substantially improve someone's survival and quality of life and the goal now for myself and Dr. Boyer and our team, what about that other 80%? So we were trying to figure out with the BATTLE trial and other trials what to do for that 80%, but we can see the light at the end of the tunnel, it is a long tunnel, but we can see it.

Dr. Roy Herbst is Professor of Medical Oncology and Pharmacology, Chief of Medical Oncology at Smilow Cancer Hospital and Associate Director for Translational Research at Yale Cancer Center and Dr. Julie Boyer is Associate Director for Translational Research Administration. If you have questions or would like to 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.