Yale CANCER CENTER answers

WNPR Connecticut Public Radio

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Experimental Therapeutics and Cancer Treatment

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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 doctors Foss and Wilson are joined by Dr. Paul Eder for a conversation about experimental therapeutics and cancer treatment. Here is Francine Foss.

Foss Let's start off by having you tell us a little bit about yourself. You are new to Yale so give us some background about where you have been, what you have been doing and what your role is going to be here at Yale?

Eder I grew up in Washington D.C., about two and a quarter miles from the National Cancer Institute Clinical Center and my mother was a nurse so she always wanted me to be a physician and that probably has something to do with how I ended up here. I got interested in oncology because it was the most fascinating and exciting field that I heard of in medical school and after quite a few years in Boston at the Dana-Farber Cancer Institute and a brief sojourn to industry at AstraZeneca, I started at Yale on July 1, 2012. The particular reason I came here is because of the incredible richness of the science and the commitment of the institution to try to get better, newer therapies for patients with cancer.

Wilson Can you explain a little bit about what experimental therapeutics are and their role in cancer?

Eder Experimental therapeutics might be broken further down into experimental and what we might call developmental therapeutics. Experimental therapeutics is trying to get new treatments for cancer using non-human settings and sometimes this is what we call a tissue culture or cancer cells growing on a Petri Dish, or animal models of a tumor. We look to try and establish the value and the safety of compounds in those settings before we even bring them to the patients. Once we have a reason to believe the compounds have a probability of success, that they are safe and we have some idea about how we would use them, we then bring them in the clinic and that's what we call developmental therapeutics. It is a very phased sort of staged way of doing it, phase one, two, and three, each of which have different objectives and different goals.

Foss Paul, can you back up and explain for the audience about how this all starts, say you identify a compound that you think might be interesting in cancer, how does that process happen?

Eder This is something that has changed dramatically in the last 20 years beginning from the first therapeutics for cancer, which actually began at Yale during World War II as part of work being done on potentially toxic agents. The original work in cancer postwar was largely discovery.

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You made animal models or you made experiential models and you looked for natural products that might inhibit their growth, or taking the few drugs that have shown anticancer efficacy before the work, and try to look for drugs that mimic them that might be better compounds for patients, but over the last 20 years with the discovery and really unraveling of the human genome it has changed entirely and now we make drugs to fit targets. So, natural discovery work goes on but has largely been replaced by very elegant models of specific targets in cancer cells, identifying specific proteins, and even three dimensional structures and trying to develop drugs that fit into those structures, so there has been a huge change over the last decade and a half.

Wilson The process that you have just described, sounds to me much more likely to have a higher probability of success with something that is more targeted as opposed to the random historical experimentation evaluation process, do you think that is the case?

Eder That is probably true, and unfortunately we are not anywhere near getting 100% or even 50% value for the kind of science we have. Cancer is a very-very complex disease and there are many things that are involved in it, and we select a single target, and once in a while nature, maybe 10% of the time, gives us a disease setting where a specific target is responsible for how this disease behaves in patients. Most of the time it is a complex interplay and sometimes just affecting one aspect is really not enough to produce clinical benefit, but overall it is quite true that we have much better ides of what we are trying to do now to improve on this process then we would have had two decades ago.

Foss Most of the cancer drugs that the audience is familiar with now are the drugs that we developed in the old days and many of those came from natural products. Can you talk about that and tell us whether there is still a role for that kind of research as well?

Eder Certainly there is, and many of the drugs that we currently use are based on the original structure of natural products, so we take these and use them as sort of a scaffold on which to build a brand new platform for drug development, but many of the older drugs still have one significant advantage over the targeted therapies of the last two decades, and that is that they cure people, and although we sometimes do not fully understand why, we know that in certain types of tumors like leukemias, germ cell tumors, testicular tumors in men and maybe to a lesser degree ovarian cancers and others, we cure patients who have fairly advanced disease and in all circumstances the most important drugs are the old fashioned “discovered drugs" that we associate with cancer and cancer therapy.

Wilson Paul, tell our listeners a little bit about how we get from the experimental to the developmental stage. It’s obviously a pretty complicated process, take us through that.

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Eder An investigator usually working on his or her own will discover a “target” a new process involved in a specific type of cancer or perhaps cancers in general, and once that is done and other investigators verify this, because nobody wants to take the risk and the plunge of this development and experimental cost if you do not have insurance that your target is valuable. We try to confirm this independently with different investigators and if that is the case then either an academic group or a pharmaceutical company will try to look at a system where they can model these targets. Sometimes it is just an isolated protein, not even cells, and they run it through a library of compounds to see which interacts with what, and once you get the first sort of hit, you then begin to modify the drug, the compound, the chemical, such that it becomes an even better inhibitor. Once that is done, you go back to a cell based system, where you have individual cells growing on Petri Dish’s and you look to see whether or not that target interaction produces desirable effects in cancer cells. If it does, you try to generalize and see, are these kinds of cells representative of what you see in human beings? Many cell lines have been present in the laboratory for five decades and they have their own characteristics, that don’t always reflect what happens in patients, consequently, we are always trying to come up with evidence of better models, better systems, and we want to look and see that we get this interaction that might happen in human beings. So once targets have been discovered, we look to see if the target is present in specimens of biopsies and surgeries from the patients that have been taken in the past. If it is, you then try to do a system where a tumor is placed into an animal and you will then try to see whether you can shrink the tumor or cure the tumor in the animal while not harming the host. So it is a whole repeat process where you try to find the drug that gives you the best therapeutic benefit, shrinks the tumor, but also is the safest. Once that is done, then there is a more complicated safety processes done in several different types of animals to be sure we know what the side effects are and to try and estimate whether the levels that are tolerable by animals will give us the affect we are looking for in cells or in animal models of tumor. Once that is done and the regulatory agencies, including the FDA and its advisory committees as well as the sponsor and the individual institutions that want to participate in human trials, review all the data and decide if this looks to be safe enough and appropriate enough science has been done to take this to patients in phase I studies, as they are called and this is largely what I am involved in, trying to determine what is the safety of the drug, what are its side effects, what's the best dose, how often should you give it, and try to determine both from patient benefit and sometimes from biopsies or blood work and other types of assessments such as imaging with x-rays or radiology, if the drug actually interacts with its target and is this beginning to show some evidence of clinical benefit. Most phase I trials will include patients with a variety of tumor types and really just insist that it be appropriate for the patient to go on an experimental treatment and that the patient is healthy enough to tolerate it. If the drug is safe, it achieves those levels that you think are going to interact with the target. Phase II trials are when all the patients have the disease that you are interested in. Increasingly, in molecular targeted therapies, patients will have a specific mutation or specific gene profile that tells us the

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drug should work in that setting, and in a phase II study, if the drug shows benefit and based on experience with drugs like this or other patients with this disease, if it looks promising enough to take forward it can then go either directly to the FDA in a setting where there is no approved therapy of any benefit, or it can go into a phase III trial, where it will be compared to the best existing therapies, and sometimes it is adding on, other times is replacing therapy. So this paradigm, this process of phase I, II, and III and it can take anywhere from 5 to 12 years and it is no reflection on the drug that is has been in clinical trials for many years. To get the safety and the benefit takes a long time.

Foss Paul this has been a criticism of the FDA obviously for a lot of things, but one of the things is how long it is taking them to approve drugs. You have described a very complicated process. Do you see anyway that process could be shortened?

Eder I think this is a very important question. I am not so sure that this really falls on the FDA. The FDA may take four to eight months to review something, which seems like a lot of time to some people but in this span of a decade or more it is only a small portion of it. The biggest challenge for us is to identify patients early so we can demonstrate that the drugs work. To show that drugs are marginally effective and the patient's were well selected, and if a lot of people showed some benefit, but some drugs which have recently been approved where they identified the patients beforehand, they do not go to phase III, they come right out of the phase II and some of them merge from phase I to II because the benefits are so striking.

Foss And that would explain, I think another issue that patients often have, which is this new drug is out there in phase I trials, why can't I get it? So what you're saying is that we are really trying to focus on very specific populations of patients that may benefit from some of these new drugs?

Eder Yes, I think at one time we started to look at drug development as a great big parade line, people marching across the drug approval line at once, and now we think of it as a spear, get the tip across and the rest will follow. We do not have to try to prove all the value initially; let's just find one setting, and once the drug is approved, we can start looking much more rapidly and simply in patients once we have got that kind of good housekeeping seal of approval from the FDA.

Wilson Paul, you have seen the situation many times where a patient may be very interested in trying to get access to a cutting edge clinical trial and some other patients are very much opposed to this. They are interested in only considering what might be considered a standard therapy, and sometimes patients often ask their doctor, is the treatment you have described experimental? I understand that it is often based on consensus, but where is that line? How do you identify when a treatment goes from being considered more of an experimental or developmental product, to

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something that is considered standard?

Eder Well standard would require that the FDA says this is approved in this indication. I think in my world with phase I drugs it is always very clear to patients. The ideas behind this are really good. The work up until now is very promising, but this is unproven as a human drug and experience would tell us we think we are right so many more times than we have actually been right, but once the drug has begun to show benefit in some group of patients, this is usually going to be phase II trials, at that point we can begin to tell the patients we do not know overall how a group of people will respond but we are seeing real benefit, at this point have some evidence about the side effects. So patients can make a better judgment as to whether or not the drug is actually something they want to participate in.

Foss Can you talk very briefly about the risk level with a phase I trial, should the patient be concerned about that?

Eder Yes, at all times. We are very clear that these are drugs of unproven benefit and we know at some point they are going to have side effects and so we always tell patients serious side effects, and even death are potential outcomes of phase I trials. The National Cancer Institute actually put together its experience several years ago, and of 13000 patients on phase I trials, the number of patients who actually derive clinical benefit is 100s of times greater than those who actually have serious side effects or even die on these studies. So, despite the fact that they are experimental and investigational, much of the work we have done to try and make them as safe as possible going to patients seems to have given us some benefit in these large experiences that we have.

Wilson We are going to take a break now for a medical minute. Please stay tuned to learn more information about experimental therapeutics and cancer with Dr. Paul Eder.

Medical Minute *There are over 12 million cancer survivors in the United States right now and their numbers keep growing. Completing treatment for cancer is a very exciting milestone, but cancer and its treatment can be a life changing experience. The return to normal activities and relationships may be difficult and cancer survivors face other longterm side effects of cancer including heart problems, osteoporosis, fertility issues, and an increased risk of second cancers. Resources for cancer survivors are available at federally designated comprehensive cancer centers such as the one at Yale Cancer Center to keep cancer survivors well and focused on healthy living. This has*

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been a medical minute brought to you as a public service by Yale Cancer Center. More information is available at yalecancercenter.org. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.

Lynn Welcome back to Yale Cancer Center Answers. This is Dr. Lynn Wilson and I am joined by my co host Dr. Francine Foss and we are discussing experimental therapeutics and cancer. Paul, tell us a little bit about some of the history behind Yale's involvement in these types of studies and programs.

Eder Well, during World War II many physician scientists were brought into the military, some serving on the frontline in battlefield situations, such as my old mentor Tom Fry. Others worked in experimental work and although the United States never used toxic gases, they prepared for the possibility that the enemy might and so a group of ships were actually taking a gas called nitrogen mustard that had been developed by scientists like Goodman and Gilman who were professors at Yale, then and later, there was an accidental exposure due to the fact that the plane was bombed in the Harbor of Bari in Italy and a number of the sailors and marines exposed to this showed significant changes in their blood counts and the physicians looking at this said, well if it makes normal blood counts go down, there are diseases like leukemias, or lymphomas where blood counts are very high, will it get rid of malignant ones? And sure enough it did and the study was only published in when the war was over, but nitrogen mustard was the first effective therapy for lymphomas and leukemias and still served into the 1980s as the basis for treatment for Hodgkin's disease and other types of non-Hodgkins lymphoma and Goodman and Gillman among others began the process of looking at these in a much more vigorous and scientific manner and so for decades Yale has been a leader in molecular pharmacology and biochemical pharmacology of anticancer agents. Pharmacology does many other things besides that, but their leadership in understanding how drugs work , how patients remove drugs, how drugs interact with patients has been something that Yale has been bringing forward for over 60 years now and something that continues to this day.

Foss Paul, you are leading a new phase I research program here at the Yale, can you talk a little bit about that program?

Eder It is going to require use of a lot of different medical disciplines. In the clinic it is not only doctors who treat patients, there are nurses that we call advanced practice nurses who are serving in many roles like doctors, research nurses, clinical nurses who treat patients. We have program managers who keep things organized and many of these studies are highly choreographed with lots of testing done and somebody has to keep this stuff organized, make sure that it gets done over and over

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again the same way, so then when we sit down and compare the results we can say, when we did these things with this experimental drug, we saw this, and so we can decide whether or not in fact the drug has value. There are data managers who work behind the scenes to collect all this information, get it organized and processed, and then it goes off to sponsors, whether they be the National Cancer Institute or a pharmaceutical company, who unravel it back the other way, to data managers to others and usually these will involve not only the physician who is actually involved in the trial, but increasingly now basic scientists who help us understand what it is we are actually looking for in patient's samples, scientists who give us constant feedback on whether or not we are pursuing the right target. We have interactions with other non-physicians such as pharmacologists who tell us how the drug is behaving, how the patient is doing with the drug, so it is a very-very large group of people, and overseeing all of this are what we call the disinterested parties, these are the IRBs and human protection committees. People who are not physicians and are not involved in the trial who constantly review things and ask, are things being done in an ethical and appropriate manner and are the patients informed of the risks, are they informed of what findings you have discovered so that they come to these decision about whether or not to participate in a trial in the most informed sense, and all of this plays a very important role in his entire drug development process which certainly contributes not only to the length of time it takes, but considerably to the expense. We always try to find ways to minimize cost, but many of these things in these very early trials, safety has got to be a consideration that outweighs all of them, and it is really necessary to do this.

Foss Paul, I just want to stress one point, you had said that if a patient is enrolled in one of these trials and there are various side effects that other patients are experiencing, there is a mechanism for patients to be informed, could you talk a little about how you keep patients informed in an ongoing fashion?

Eder Well, the most honest thing we do is, you know, many of these times these trials are to be done at multiple different institutions because they are time and labor intensive. So, we meet every week to discuss with the other clinical investigator, the doctors, and nurses, what do see, what are we seeing, together that looks like might be related to the study drug. Late stage cancers can be complicated. The patients has complications of the cancer, there are complications of other drugs, and they get the same influenza that the rest of us get sometimes, even more frequently, so we constantly try to talk to each other and then it is important for us to every week talk to every patient in detail about what he or she has experienced, we are telling what we have seen and if we have seen enough then we can conclusively judge this is related to the drug, we will take what is called the informed consent and re-write it to let them know this is what we were seeing now. Unfortunately we can not give them the kind of confidence we do with standard treatment where we can tell our patients there is a 2% chance that this might happen. In early clinical trials, we

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can often say, we have seen it, but whatever we do, the most important part is actually talking to the patients and tell them what it is we are seeing before they sign the document, so they trust that they are getting the best possible information as soon as possible about these things.

Wilson Paul, as you mentioned there can sometimes be significant expense associated with doing these studies, and you had mentioned the term, sponsor, could you tell our listeners a little bit about that process, whether it be the National Cancer Institute or pharma, or a foundation. What is the process that one goes through to try to get these studies funded?

Eder One of the things that has evolved over the last few years is what we call investigational cost versus the standard cost, so for a doctor to see a patient, talk to a patient, get routine blood work to monitor their cancer or any treatments, these are what we call standard cost, anything that is above and beyond that, extra x-rays, extra EKGs, extra blood work, extra visits, these are considered research costs, so those are attached onto that and I am sure as some patients are well aware, one of the biggest expenses now in clinical oncology is the cost of drugs, so in fact subtracting that cost because these are investigational drugs that are not billable or reimbursable, the actual cost somehow gets compressed in terms of the actual patient care cost, but the cost of all the personnel that are involved have to get passed on so it is a big deal and a sponsor will give a certain amount of money back sum, what we think the actual cost are. The NCI or the National Cancer Institute usually gives us a lump sum. They will give us a certain amount of what we call funding from year to year and say you need to do 50 to 100 patients and here is the money you get to do it and foundations will sometimes do the role the same. Usually foundations aren't going to be involved in early phase one stuff because of the complexity and really the novelty of these compounds, you have got to be somebody with the resources of a pharmaceutical company or the National Cancer Institute to really sponsor that, but foundations help us sponsor phase two and three trials.

Foss Paul, we talked about different types of cancers and some of these trials target one cancer or another, are you covering a broad spectrum of cancers here, are there certain cancers that more frequently would be the type of cancer that would be treated with a phase 1 drug or can patients with any cancer think about these kinds of trial?

Eder Most phase 1 trials, Francine, really are agnostic. For the most part when they first start, it is open to all comers. We think we are smart, but we are actually humble enough to know that we are not always as smart as we think and sometimes the target we intend is not the target that turns out to be the most valuable one. Early on we will do trials that take essentially all comers and the real criteria again is, is it ethically appropriate? You are not currently doing something else that is

better for you and you are well enough to actually undergo the trial with the risks that are associated with it. So, for most phase I's we take all comers and the exclusion criterion is based more on the patient's health than anything else. Phase 2 and 3 trials will be very selective in terms of their patients, they will have a single tumor type or increasingly, within a tumor type, a specific target we are interested in. In breast cancer, the breast cancer associated gene is BRCA, and there are trials where not only do you have to have breast cancer, but you have to have specific changes in these genes in order to get on a trial because that's where we know the drug is going to work. It does not mean we would not look elsewhere, but we have sort of taken it the other way of saying, let us try to demonstrate benefit on a large number of breast cancer patients and then we will see who are the most likely to benefit. We now try to use science and say, these are the most likely to benefit, let's study them first and let the other patient come along. Because of the association of the new cancer centers here, patients are identified by their oncologist at there original point of entry into cancer care, if at some point these well trained oncologists who understand that we have these trials available, may refer their patient to Yale for the specialized aspects of this, and one of our challenges is of course to be able to get these patients in appropriately and when we think it is safe to send them back to the community to do that, so they don't spend too much time here, but what else has changed in the last 20 to 25 years it that it is very rare for us to admit a patient for a clinical trial. This is all outpatient, so they spend a lot of time with this, but we do not have the same restrictions we used to where drugs were always given in the hospital. Even now in Japan, the standard is you need to be hospitalized for 28 days to get your therapy even if you are taking a pill every day. The Japanese I'm sure understand that this is not a very cost effective way to treat people.

Foss I just want to make sure the audience realizes that patients who go on to one trial are not necessarily at the very end in the course of their treatment, in another words, traditionally we think about exhausting everything else and then going to a phase 1 drug, could you just elaborate a little bit about that?

Eder I think that is a very important point. You could walk into a phase 1 clinic and you might think you are sitting down in the lobby of the Hilton because people look just like everybody else does, it is very important for us to know the patients are physically well, but what has changed is we have begun to understand what therapies work, when they stop working, and instead of giving patients treatment which could best be described as futile, patients are informed early on that there is an alternative and that they can try these trials and see if they benefit. In an informed community such as Yale, but also in other cancer centers the physicians understand the limitations of our current therapies and they try to identify these patients early, when their health is still good

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enough that they will qualify for trials, and at least present the option as opposed to reaching a point where it might be appropriate to consider an experimental therapy, but their health is too compromised to get on a trial.

Wilson Have we seen changes in the trends of percentage of cancer patients who are enrolled in clinical trials or has that been pretty stable over the last 10 to 20 years?

Eder I think that has been pretty stable over the last 10 to 20 years. At research institutions such as Yale perhaps one in six to one in five patients actually goes onto a clinical trial, this is going to be different in other areas, but many times part of that reflex is that we have better therapies, and patients don't need to get to the stage of a clinical trial. In pediatric tumors parents take their children immediately to clinical trials and say, I do not want to take any chances that my child is not going to benefit from the best cancer therapy there is. 80% of children go on clinical trials. It is somewhere in the range of about 3% to 5% of all adults and at Yale it would be somewhere about 17% to 20%, but nationwide, the number of patients who actually go on trials is very-very small.

Foss We have just one minute left and I wonder if you could tell us about any of the exciting advances that you see coming in the next year or so at Yale Cancer Center?

Eder I think one of the areas that Yale has been a substantial pioneer has been in recent innovations in immune therapy. This has been an area of interest for cancer researchers for over a century, to understand why it is that these foreign cancer cells are not rejected by the body the way a transplant would be, and the reasons have been largely that the cancer cells are of course derived from the host, so they are more alike than unalike but we have begun to realize that cancer cells actively screen themselves from the body's immune system, kind of like the old cloaking device of Star Trek Times, and now we have begun to understand what it is that actually makes this happen. Drugs have been developed that unravel this cloaking device and now the cancers are the visible to the immune system and drugs like PD-1 and PD-1 ligand inhibitors were the talk of this year's cancer meeting. So patients with tumors like lung cancer who where never really thought to be sensitive to immune therapy, have shown real benefit and these are the kinds of treatment that at this point are given to patients with late stage disease, we can reduce the size of the tumor with surgery, radiation or existing drugs. These are almost certainly going to be much more effective in that setting than they are as a single therapy in patients who had alternatives that had been exhaustive, so that is probably the single most exciting thing. The other thing that is exciting is the increasing what we call segmentation of cancer into subtypes, and it is less important now that your tumor is a lung cancer or a colon cancer, or a breast cancer, then what is the mutation that

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drives your tumor? So drugs are no longer just looking for cancer types, they are looking for specific mutations and increasing work has come in areas like lung cancer, lymphomas, with drugs that target a specific subset of patients with these tumors, so that we can put the patient most likely to benefit on a new treatment and we can try to find out who really needs the therapies.

Dr. Paul Eder is an Assistant Director for Experimental Therapeutics at Yale Cancer Center. 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