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DNA Sequencing and Translational Research

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Yale Cancer Center Answers

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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 1-888-234-4YCC. This week, doctors Foss and Wilson welcome Dr. Bonnie Gould-Rothberg. Dr. Gould-Rothberg is Assistant Professor of Medical Oncology and she joins us this evening for a conversation about translational research. Here is Francine Foss.

Foss Let us start off by having you tell us a little bit about what translational research is.

Gould-Rothberg In my interpretation, translational research is bridging the gap between the basic scientist, PhD, and all of the research that is going on at the laboratory bench. The clinically oriented medical doctor, and the interaction with patients, throughout my experience in medical school, I found that these two groups of people tend to talk very different languages and the goal of translational research is not only in figuring out how to take the exciting discoveries from the laboratory bench and bring them into the clinic in a meaningful way that the physicians are going to be able to use them, but in a way to translate the language of how the basic scientists are talking and make it accessible to the physicians so that they understand and appreciate, and can collaborate better. It really is, as I said, bridging the gap between these two very distinct camps.

Wilson That sort of seems like an obvious concept, it makes a lot of sense, is it something that has not been going on forever? Would you say it is more of a recent phenomenon?

Gould-Rothberg I think it is a more recent phenomenon in more mainstream research. Fifteen years ago when I started working at CuraGen Corporation, I was the founding scientist of our pharmacogenomics program. Back then, we were doing translational research. We were looking for signatures and drug responses in animals that would suggest toxicity profiles in susceptible humans. We were starting to think about looking at individual genotype variations or single-nucleotide polymorphisms that would allow some people to be more susceptible to side effects, or some people to be more susceptible to having a positive or negative response from a given drug, but we were at the time on the cutting edge of this field. The whole concept of translational research and personalized medicine really evolved with the targeted therapies in cancer and in other diseases, and now that you had a drug that would only work in a specific subset of patients, you had a responsibility to identify more specifically which patients those would be, have companion tests and think about, what are other specific ways of targeting cancer?

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Foss Bonnie, you are relatively new to this position at Yale, but you have been at Yale for a long time. Can you tell us a little bit about your background and how you got interested in this area?

Gould-Rothberg I actually arrived in New Haven in 1990 as a first year medical student at Yale University, stayed at Yale for my residency, got married, and pretty much have stayed in New Haven ever since. When I was initially working at Yale, I knew that I wanted to ultimately go on for an MD and a PhD. Being a Canadian transplant, however, I was not eligible for a lot of the available funding and my parents looked at me like I was crazy and said, well you know we are going to pay for 4 years of this, but 7 years is out so you are going to need to think of a creative way for figuring out the PhD part. Back in the early 90s, most of the PhD programs were focused around in vitro science, science in the test tube or in the Petri dish. A lot of research was going on to understand physiology at the level of ion channels, some of the basic signal transduction research, and a lot of cell culture. I just was not resonating with that type of research. However, in the mid 90s, I went to help out my husband's new company, CuraGen, and he would come home at night with printouts of differential gene expression profiling lists from experiments, and he looked at me and said, "Bonnie, you're an MD, you've studied pharmacology, you've studied physiology, we have three rats treated with compound X and three rats that weren't treated with the compound. These are the genes that are differentially regulated in their fat tissue. Can you tell me what's going on here?" And I was just totally fascinated by having a list of 200 genes and being forced to draw upon all of my basic sciences as well as my clinical science knowledge to try and find patterns, and just being able to sort through large groups of data, for me it was really, really exciting and interesting and in 1997 I went to go work at his company for 5 years. That sort of fostered my interest in doing large-scale genomic science and doing large-scale science in particular, and when I came back to Yale in 2003 in the Masters of Public Health Program, I was very excited to learn that a lot of the research that we had been doing at CuraGen fell into the growing category of what they were considering as molecular epidemiology, looking at trends of either differential gene expression profiling or single-nucleotide polymorphisms across large populations and looking for associations with those polymorphisms for certain outcomes or certain clinical characteristics, and it was at that point that I decided that I was not only going to stay on at Yale and get a PhD in molecular cancer epidemiology, but that I really wanted to build a research portfolio around this.

Foss Can you tell us what these single-nucleotide polymorphisms are? We have talked a little bit about those with some of our other guests, but just to clarify for our audience, what are these changes in genes and how do they impact which patients get disease and how patients respond to drugs?

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Gould-Rothberg We all have DNA, our DNA is made up of letters A, T, C and G, and when these letters are strung together, they form combinations of proteins. Each gene has sort of a standard way that occurs most commonly in the population, and there are also opportunities for what they call single-nucleotide polymorphisms, where instead of having an A in a certain position, you have a C, a T, or a G, and substituting out the A for any of these alternate letters ever so slightly changes the structure of the protein that then gets produced from the gene, and in many cases this change is imperceptible, the gene works the way it should, but there are some cases where the slight change in the confirmation of the protein is enough to reduce its sensitivity to a drug or to reduce its activity in combining with another gene, and in these situations, there is a slight variation in physiology. To be sure, a single-nucleotide polymorphism is considered to be a healthy variation. People are not sick because they have a single-nucleotide polymorphism, but it may confer a small increase in risk or an increase in protection when we are talking about a disease of interest.

Wilson Tell us a little bit about some of your interactions and some of your goals with folks who have a strong interest in translational medicine, personalized medicine, such as Dr. Roy Herbst, for example. Tell us a little bit about some of your goals, projects, things you have in mind?

Foss I am going to be working on two very different research focuses while I am here at Yale. The first aspect is going to be my own research and looking for molecular prognostic markers in cancers of variable prognosis. For example, melanoma or early-stage lung cancer, where even if people are diagnosed at an early stage and the surgeons are able to take all of the cancer out, and they think they got it all out for both stage II melanoma and early-stage lung cancer, 5-10 years down the road, 50% of the people will still have had a recurrence even though the surgeon says, we have got it all out. Unfortunately, for each of these cancers, the risk of toxicity associated with giving adjuvant chemotherapy, given the chemotherapy choices that we currently have now, is too high to say, well, let's just give everybody chemotherapy and hope for the best. The current plan now is, we tell people, we are going to follow you clinically, we will check you every couple of months, and if there is no sign of recurrence, we will be fine. But that is a very nerve-racking choice for patients, and if we can identify at the time of diagnosis additional risk factors that make it more than a 50-50 proposition we can say, well, you have a higher likelihood of recurrence, let's maybe give you the chemotherapy upfront, or no, your risk of recurrence is lower, we are not going to stop following you, but we really do not think you would benefit from the chemotherapy to be able to do that and to identify what these additional stratification variables are. That is going to be one aspect of my research. The second aspect of my research is going to be around creating biobanks for cancer samples at Yale.

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Wilson There is some pretty high-tech stuff that is involved with this. This is not the kind of work that would typically go on at every hospital in Connecticut, or even at many places around the United States. It sounds like Yale has got this infrastructure and experts like yourself to offer these kinds of trials and modalities for patients. Would you agree with that?

Gould-Rothberg Yeah, I think so. I mean at this point being able to develop these models requires a certain amount of sophistication, being able to implement the models requires a certain amount of sophistication, but at the end of the day our goal is that in 15-20 years, hopefully sooner, to be able to develop tests and tools that are easily implementable even in the community. Obviously, you want to have well-trained physicians who know how to interpret the results of these tests and who know how to administer them correctly, but we really want to make these tests accessible more broadly.

Foss You are talking about a disease like melanoma that is very common and trying to identify factors that would be more favorable. Do you need to look at large numbers of patients, how do you actually do that kind of a study?

Gould-Rothberg That is a really good question and that points to one of the most important aspects of doing clinical research and doing epidemiologic research, and while you think that melanoma is common, melanoma actually will occur in only about 65,000 patients across the United States, and perhaps maybe another 1,200 per year in Connecticut alone. At the same time, you think that is a lot. We are talking about stage II melanoma, which the group of patients that have that 50-50 risk. That maybe is only about 400 of all the melanoma patients that are going to be diagnosed. And yes, in order to do these studies, you need sometimes several thousand patients in your study. In order to enroll these patients, we actually rely on the good will of community physicians that when they encounter a patient, they are willing to refer them to a study. We also work very closely with the Connecticut Tumor Registry. Yale is a participant in what we call the Rapid Case Ascertainment. So, as physicians in the community report new cases of cancer, which is mandated by Connecticut Law to the Connecticut Tumor Registry, we are able to very quickly identify who those patients are, but at the same time, we still need to contact their primary physician and ask for permission to contact the patients. It takes time.

Foss Bonnie, is this a two-way street? Say if a patient has a disease like melanoma, is there a way that they would know to contact you as opposed to say being identified through the tumor registry?

Gould-Rothberg In fact, studies should be posted on our Yale websites. We should be able to communicate

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out in the community that we are interested in enrolling patients. If a patient approaches us or their physicians, saying, I am interested in participating, that would be great. That is the ideal situation.

Wilson We are going to take a short break for a medical minute. Please stay tuned to learn more information about translational research with Dr. Gould-Rothberg.

*Medical
Minute*

This year, over 200,000 Americans will be diagnosed with lung cancer, and in Connecticut alone, there will be over 2,000 new cases. More than 85% of lung cancer diagnoses are related to smoking, and quitting, even after decades of use, can significantly reduce your risk of developing lung cancer. Each day, patients with lung cancer are surviving thanks to increased access to advanced therapies and specialized care. New treatment options and surgical techniques are giving lung cancer survivors more hope than they have 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 lung cancer. An option for lung cancer patients in need of surgery at Yale Cancer Center is a video-assisted thoracoscopic surgery, also known as a VATS procedure, which is a minimally invasive technique. 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 Broadcasting Network.

Foss Welcome back to Yale Cancer Center Answers. This is Dr. Lynn Wilson and I am joined by my co-host, Dr. Francine Foss. Our guest today is Dr. Gould-Rothberg, and we are discussing translational research.

Foss Bonnie, before the break you were telling us about some of the things that you were involved with, and I know that you are working with Dr. David Rimm. He has some very cutting-edge technology. Can you talk a little bit about that and what your interaction is with Dr. Rimm?

Gould-Rothberg Dr. David Rimm has been tremendous. I joined his lab back in 2006 when I was doing my PhD and actually created a unique PhD program for myself that bridged both the more basic molecular biology disciplines and the epidemiology and public health programs, and actually did the bench work in David Rimm's laboratory. David Rimm, in the early 2000s, developed a new technology called the automated quantitative analysis, or AQUA technology, that is based on quantitative immunofluorescence. We're working with proteins in a tumor. Again, tumors have DNA, DNA then makes protein, and it is the protein that is actually the

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building blocks of the tumors. The protein runs all the regulatory mechanisms of all our cells, and when these protein regulatory mechanisms get appended, these are what we think contribute to cancer. Dr. Rimm's laboratory has been very interested in identifying proteins that get dysregulated, and in concert with their dysregulation, poor outcomes, this is what we call prognostic markers. So, we can have a hundred tumors of lung cancer that all look the same under the microscope, but when we start to look at levels of protein, we can see that despite the fact that they all look the same, cancers that may have higher levels of this one protein tend to do better and cancers with lower levels of the same protein tend to do worse or vice versa. I joined David Rimm's laboratory to do a project in melanoma. We actually did several experiments. The first project that we did was to make an educated guess of which proteins we should be focusing on together. We sat down and did a whole review of all the literature that is out there and organized that, going back to my love of taking long lists of genes and putting patterns into them, but more exciting is Dr. Rimm had began with Erin Berger who is the prior graduate student in melanoma, looking at a panel of over 30 genes and 30 proteins in melanoma using his quantitative immunofluorescence, which is where we are able to measure exact levels of the protein in the different tumors, and whereas Erin was able to measure and assay these 30 plus proteins, we needed to go back and sort of analyze the data and put together a compelling story. As part of my PhD, I actually added to Erin's set of proteins, but then performed a comprehensive analysis looking for sets of proteins that would be prognostic, and in 2009, we actually had a fun paper that came out in the *Journal of Clinical Oncology*, reporting on a prognostic model in melanoma where we combined the expression levels of five proteins into a single measure, and patients who had four or five of the markers that we were looking for, tended to do much better than patients who only had three or fewer of them.

Wilson Bonnie, have you done this kind of fascinating work in other systems such as lung cancer, or do you intend to do that? What else is going on besides melanoma in your work?

Gould-Rothberg I have started a program in lung cancer. Most of my effort in lung cancer to date has been working with Lynn Tanoue and the Thoracic Oncology Program at Yale. For the last 2-1/2 years, I have been chipping away, setting up collaborations with the lung cancer physicians and more broadly across the Cancer Center to set up the lung cancer biorepository. A lot of the work really has been in identifying the best practices for biobanking, and bringing those to Yale and setting up that infrastructure at Yale so that when we archive samples, they are there for future use, and what we expect that we have put in the bank, we can then withdraw later on. I also have additional research programs going on in some orphan disease work. I have been working in tuberous sclerosis and lymphangiomyomatosis, which is a rare lung disease that causes cystic degeneration in the lungs and proliferation of a smooth muscle-like

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cell and the potential space between the alveolar wall, which is the air sacs and the blood vessels, which basically makes it very hard for oxygen to get into the lungs and carbon dioxide to get out. The patients have a hard time breathing. LAM, as it is called, is found in women with tuberous sclerosis for the most part and also occurs sporadically in women with no history of any disease, and the sad part about LAM is that if you are going to get it, it occurs in women in their early 20s to mid 40s. It is very devastating and I am very excited to be able to work with the community there.

Foss A lot of your work depends on tissue, and you mentioned tissue banking, can you tell us, what is the importance of tissue banking? What is a tissue bank and how does one go about building a tissue bank?

Gould-Rothberg Francine, as you mentioned earlier, it is very complicated and involves setting up these large clinical studies, and that is the most important thing to remember. Setting up a clinical trial or a large epidemiologic study takes up patient's time, takes up a lot of the physician time, and takes up a lot of resources. They are very expensive. Each study is set up to ask a main question, or a primary hypothesis, but once we have gone through the effort to assemble several thousand people over a 3- or 4-year period and ask them all these questions and collect all this information out of their medical record, it would be a shame then not to have any additional resources left over to be able to answer scientific questions that a good scientist thinks about 2, 3, 4, or 5 years after the study has ended. So, one of the main goals of setting up these biobanks is to be able to leverage all of the value that we have already put into these studies in the future to create a resource that additional physicians and additional scientists can tap into and go back and revisit these same-study populations. The most important thing about a biobank is that what you deposit into the bank, you can withdrawal it back, and like any bank, you do not want the bank to go bankrupt, you do not want to go back to the bank and find out that they have put all the money into bad loans and it is not there when you need it. The equivalent thing we found out a couple of years ago with a lot of biobanks is that you need to know how to store the material. We used to think that you can put something in the freezer and it is there perpetually. Unfortunately, what we have since learned is that you cannot just put things in any old freezer. Even when bio tissues are frozen, the degradation process is still going on ever so slowly. While things will rot much quicker at room temperature than they will in the fridge and they will rot even slower if you put them in the freezer at home, if you leave things for 4 or 5 years in the freezer and try and take it out and defrost it and have dinner, it is not as good as something that you just put in the freezer last week, and the same thing goes for tissues. We have learned that if you take tissues and put them even at -80 degrees, which is the temperature that you see outside

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an airplane when you are flying across the country, 5 years later you take out that material to use it, and you find that it has mostly degraded and is not usable. The standard now is to put samples in liquid nitrogen, which freezes them at -160 degrees.

- Foss A lot of the trials that we are doing now in the NCI cancer cooperative groups, all of those trials ask patients for tissue to go into tissue banks, and they specifically ask if that tissue can be available for other studies beyond that clinical trial, and I think a lot of patients do not really understand the importance of that piece of it.
- Gould-Rothberg I think that is right on. People are scared that their information is going to be used and sold to the highest bidder, and in fact, that is not going on. We are all working towards the same goal, which is to improve the human condition, and it is so important, that tissue, that that blood samples, tissue samples be available to researchers now and in the future, and that we have the ability to do not only the projects that we are proposing and specifically asking about, but also projects that we may think about in the future. I know that people are getting a little bit more nervous with the new genome technologies where people are now saying that they can sequence an entire genome in a very short period of time, and we can start to learn about some of the nuances that may or may not cause disease, but just because you have a certain variant or certain single-nucleotide polymorphism, it does not mean 100% you are going to have a certain disease. Some of them at best suggest that there is a small increased chance, but it is not 100% black and white certain, and we don't know enough information by sequencing your genome on anybody else's genome how to draw specific conclusions about you, and the ability to not use the sample because people are nervous about it, is probably going to cause more disruption to medical research than it is going to do to protect anybody.
- Wilson Obviously your work is really important, and if it was easy, everybody would be doing it. You have touched on some of the things, but what are the biggest challenges for you when you come to work every day?
- Gould-Rothberg If I thought about it as challenging, I probably would not get up in the morning. It is a tough question. I thoroughly enjoy what I do. In the last few weeks, I have had the distinct pleasure of setting up my laboratory and one of my most proud accomplishments is that a big crate came with a piece of apparatus, and I looked left and right and there were no big burly guys that were going to take the crate apart, and I did not own an electric screwdriver, so I borrowed a regular Phillips-head from the lab next door and spent 45 minutes unscrewing the box, only to find out that the machine inside was broken and then had to spend the next half hour on the phone with the provider arguing that you guys have to take this back because

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I have spent good money on it, and I was finally able to get somebody to come and assemble it and put everything back in the box and assemble the box back, and the gentleman looked at me and said, "You took this whole thing apart by hand?" And I said, "Yeah." He said, "These are really long screws, you did that by hand!" So it is the little challenges and it is the little victories, and sometimes the victories come when you have an exciting paper that comes out, and sometimes they come because you have been able to take a piece of apparatus and get something set up and learn to do something that you did not think you knew how to do before.

Foss A lot of the things that you are probably learning in the lab are not going to have an impact in the clinic for weeks, months, even years. How do you develop that sense of gratification about these new findings?

Gould-Rothberg I think it is just exciting to be able to learn something new about science, about the way the human body works, about the way the human body may or may not interact with the environment. A lot of what I am interested in is not just the molecular pieces, the genetic pieces, but how we interact with the environment, what our lifestyle choices that individuals, cancer survivors, can make that may improve their survival, and are there certain subgroups of patients that benefit from certain lifestyle choices such as a healthy diet and good exercise more than others? Just being able to understand these things is gratifying. Hopefully, over the years, we will be able to bring these into the clinic, but it is exciting enough just to be able to say, well, here is an idea that you can move forward with.

Dr. Bonnie Gould-Rothberg is Assistant Professor of Medical Oncology at Yale School of Medicine. 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.