Hosts

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Yale Cancer Center Answers is a weekly broadcast on WNPR Connecticut Public Radio Sunday Evenings at 6:00PM

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Welcome to Yale Cancer Center Answers with your hosts doctors Anees Chagpar, Susan Higgins and Steven Gore. Dr. Chagpar is Associate Professor of Surgical Oncology and Director of the Breast Center at Smilow Cancer Hospital at Yale-New Haven, Dr. Higgins is Professor of Therapeutic Radiology and of Obstetrics/Gynecology and Reproductive Sciences, and Dr. Gore is Director of Hematological Malignancies at Smilow and an expert in myelodysplastic syndrome. Yale Cancer Center Answers features weekly conversations about the research, diagnosis and treatment of cancer and if you would like to join the conversation, you can submit questions and comments to canceranswers@yale.edu or you can leave a voicemail message at 888-234-4YCC. Tonight, you will hear a conversation about blood disorders and cancer with Dr. Stephanie Halene. Dr. Halene is Assistant Professor of Medicine and Hematology at Yale School of Medicine. Here is Dr. Susan Higgins.

Higgins
I think what a lot of people like to learn or hear about is how their physician got interested in the particular field that they are in. Maybe you could tell us a little bit about your story.

Halene
It’s a bit of a long story and a story from far away. But I am a clinician scientist. That means I take care of patients part of the time, and the other part I spend running a lab where we research the diseases of our patients. My particular interests are in a disease called myelodysplasia, and also acute myeloid leukemia. In myelodysplasia, the bone marrow that makes all the blood cells of the body fails and patients suffer from low blood counts, infections, fatigue, bleeding. In acute leukemia, this all happens out of the blue, very rapidly and those patients come to the hospital very ill. How did I get into this? It is actually a very personal story. I lost my father to cancer, and that was many years ago in Germany, and at the time he was sick, one of the growth factors that keeps the blood counts up when patients get chemotherapy was not approved there, but our physician knew about it and so we were faced with this question about can we get, what can we do, and we ended up going through a veterinary pharmacy imported into Germany and gave it to my father, and it allowed him to tolerate the chemotherapy better. What that meant for me at that point was, I had to get involved in advancing things, I had to get involved in research, and then during my studies, a wonderful thing happened where a physician here at Yale, Dr. John Forrest, very enthusiastic in training young people, got me over to the US, got me to Yale where then he was doing clinic rotations and a lot of research, and he was in nephrology but I did a rotation in hematology and met two incredible mentors, Dr. Thomas Duffy and Dr. Joel Rappeport, and when I worked with them, I was just amazed by their empathy for patients, by their unconditional treatment and love for the patients.

Higgins
And I think one of the Smilow awards was just given to Dr. Duffy, as a lifetime achievement award and he is one of the pillars along with Dr. Rappeport who have trained generations of physicians and often those are the people that influence us early in our career, so it’s fascinating to hear about your interaction with them. You mentioned the myelodysplastic syndrome and AML, and this I think is sort of a vague notion for the public, things that happen in the blood and a lot of people don’t understand how blood cells are made and what happens in the bone marrow. Maybe you could give us a little educational moment about that.
Halene Happy to. If you think about the stem cell, the stem cells are very important cells in our body and it sits in the bone marrow where it is being very well taken care of. If you think about the cells in our blood, the red cells carry oxygen, the platelets keep us from bleeding, the white cells fight infection; those have to do a lot of work and they get used up. And so, every day the body has to make billions of these cells and all these cells come from a very few stem cells that sit in the bone marrow. If you now think about how cancer happens, think about the stem cell as the original book, and now you want to get a book to everyone, you need to print a lot or write a lot of books, and imagine this book now having to be written a billion times every day. So, it does not matter how good the proofreaders are, mistakes are going to happen and a lot of mistakes are not going to be important, they are going to get fixed or they are just not noticed, nobody cares about them. But imagine a mistake happens in the book that is either really, really bad or really, really good. That mistake is going to go viral and suddenly all the books are changed and that is kind of what leukemia is, what cancer is. It is maybe one cell, one book that goes wrong and suddenly takes over the whole system.

Higgins You have some particular interest in things that you are looking at in your lab, we would love to hear about some of that.

Halene We kind of approach myelodysplasia, MDS, and leukemia in two ways; one is that we study a particular protein that is altered in about 30% of patients with a soft type of myelodysplasia, and we perform all sorts of very technical experiments to figure out how is it functioning wrong, what does it do, how does it interact with other things that went wrong and ultimately of course is there something we can do about that wrong protein to make the disease better or even cure it? The other way we are looking at the disease – what we have learned over time, is that every patient’s disease has a unique aspect to it and we know that one type of treatment, this aggressive chemotherapy, does not work for all patients. It is also very toxic and so definitely does not work well in elderly patients, and so the goal is to identify specific abnormalities for patient diseases that we can then target and that is where this term targeted therapy comes from, and what we do in our laboratory in collaboration with Richard Flavell at Yale, we study individual patient’s MDS, individual patient’s leukemias in a preclinical and an animal model that then allows us to test different treatments alone and in combination to see what works best.

Higgins I think a lot of people are not aware of just how much ground work is laid before you even get to the point of a clinical trial with these preclinical models, various animal models and for many disease sites and therapies that takes many, many years correct?

Halene It does take many years and it takes a lot of joint effort from people in all sorts of specialties. You could think, okay the physician conducting the clinical trial is the person, but you have to remember that even the person who developed the drug did that based on knowledge that a very
large group of researchers generated, and sometimes you would think that you only have to look for the things that in the end seem to very directly lead to a treatment, but we have to remember that we need to understand a lot of mechanisms, we need to understand a lot of details to develop these therapies so that they are specific, they do not affect other cells, they do not wreak havoc in a different way that we don’t expect. So it takes a universe.

Higgins

And then we need this special group of clinician scientists, who know both halves of the game, what takes place in the lab and what takes place in the clinic with actual patients. Can you talk a little about what we call MD/PhD’s, clinician scientists and their importance right now, especially in this, I think, golden era of targeted therapies. I think you are a great example of that, but a lot of people they look at people as either scientists or physicians. How do you like having both of those hats?

Halene

That’s a very good question. I absolutely love it because when I go to my laboratory, I bring my patients faces with me. I remember them when I do what I do, and in particular, when things do not work out in the laboratory, which happens a lot because we are not doing the things that are already known, we are always pushing the frontier, we always move one step further into the unknown, sometimes we get frustrated and think, why on earth am I doing this, but to remember somebody who is suffering from the disease, whose relatives are suffering from their loved ones disease, that really keeps you going in the laboratory. The role of a clinician scientist is interesting and I think it is essential and one of our jobs here at Yale is to train young people in that direction because treating patients, but also having a pretty good idea of basic science allows you to ask the right questions. It also allows you to talk to both sides, so it allows us to talk to the very, very superb basic scientists who are absolute pros at incredibly difficult methods, concepts, competition analysis, and then also talk to full-time clinical colleagues who think about the patients all day long, but when it comes to understanding the mechanism of a molecule, they just simply don’t have the time. And as clinician scientists, we are privileged. We are also a bit at risk I think of dying out because of this era of funding. Once you have to split your time between more than one thing, you may lose out and I think that’s where everybody’s efforts to create a good funding environment, foundations that have transformative ideas that understand that collaboration is key, people are so willing to pay their taxes to support research, people who donate to organizations that fund researches, it is wonderful and essential.

Higgins

I think there is a small percentage of all physicians who can wear all those hats and have the ability to talk to the scientist, talk to each other as clinicians and then also translate that into trials and discuss that with patients, that is a really great skill set, but that skill set, as we discussed, has to be nurtured and ingrained in people by the institution, has to be valued also by the philanthropists now that we have an era where funding for the labs and for all of the people behind these experiments and trials is dwindling quickly.

Halene

Definitely.
And even your lab, I don’t think people even understand when you go into the lab how many people you have behind that machine.

That’s correct.

It’s like a little industry of your own. You have postdocs and maybe you could tell us what goes on in a lab for a person like yourself, a clinician scientist.

In the laboratory, everything starts with an idea and that idea comes in general from reading a lot, talking to people, and then once you have an idea, you want to make sure that it is a good idea, and that involves more reading, more discussions with people who are knowledgeable in the field. Then when you decide that yeah, it’s a good idea, we try to do in a way, the simplest but most meaningful experiments to assure we are on the right track, and that’s where the postdoc technicians, students come in where we develop methods or we learn methods from other people and once we have those first experiments that tell us, yeah it’s a good idea and it’s going to lead us a step ahead or a step forward, then comes this part of how are we going to do this? How can we afford it and pay for the experiments? How can we pay for a person to pursue that question, that idea, and that is when we then apply for funding. If we are lucky, or we convince the scientific community that it’s a good idea and that we have the skills and the support to pursue this idea, then we get the funding and then a lot of work starts. And every day we approach the idea, we approach the question from all sorts of sides to make sure it is sound. Then, sometimes, we discover something we totally didn’t expect, but we then have a good day, and we really bring the science forward and it’s extremely exciting and as I said, thinking about the patients we could eventually benefit, that’s what keeps us going even on bad days.

That’s great, and I think that bridging of the science and the patient care, is a great idea, and we are going to return to that in a moment, but right now we are going to take a short break for a medical minute. Please stay tuned to learn more information about hematology with Dr. Stephanie Halene.

Breast cancer is the most common cancer in women. In Connecticut alone, approximately 3000 women will be diagnosed with breast cancer this year and nearly 200,000 nationwide, but thanks to earlier detection, noninvasive treatments and novel therapies, there are more options for patients to fight breast cancer than ever before. Women should schedule a baseline mammogram beginning at age 40 or earlier if they have risk factors associated with breast cancer. Clinical trials are currently underway at federally designated comprehensive cancer centers such as Yale Cancer Center and at Smilow Cancer Hospital at Yale-New Haven to make innovative new treatments available to patients. Digital breast tomosynthesis or 3D mammography is transforming breast screening by significantly reducing unnecessary procedures while picking up more cancers and eliminating some of the fear and anxiety many women experience.

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Welcome back to Yale Cancer Center Answers. This is Dr. Susan Higgins, and I am talking with my guest, Dr. Stephanie Halene about blood disorders and cancer. Stephanie, we were just discussing some of the things that you do as a clinician scientist in the lab and how exciting that is. I think one of the products that has come out of a lot of the research in the labs are these targeted therapies and I think we are in sort of the golden age, entering into the golden age of targeted therapies and for the types of cancers that you treat, these are especially important. Could you tell us a little bit about that?

Up until not too many years ago, the mainstay of treatment for leukemia and myelodysplasia really was, and partly still is, very aggressive chemotherapy with 2 or 3 agents, and my mentors had been using those during their training, and those are just sledgehammers, but generally toxic to the cells, but that also means that they are very toxic to the body, toxic to the patient and make the patients very sick. But they work. So, with all the knowledge that we have gained over the past decades about leukemia, when it was first discovered, it was just an anatomic description, the bone marrow looks white-greenish, so not good instead of red. Now, we have a totally different understanding of what is going on in the bone marrow, what is going on down to the molecular level in the cells. So, what drives that cell to be bad, to take over everything? And those drivers are proteins, they are molecules in the cell, and when they are good, they do very important things, but they go bad and suddenly these cells no longer listen to any of the control elements in the body. They no longer do what they are supposed to do, they are always on, they don’t turn off. And these targeted therapies take advantage of the abnormalities in those proteins and the small molecules specifically attach to the protein in those areas where they are mutated, so where they are abnormal and turn them off. If you are really, really lucky, those targeted therapies only turn off the protein that is abnormal and they don’t turn off the normal protein in the cells. But even if that is not the case, our body can sometimes afford to turn off that protein and even the normal parts a little bit, and so suddenly the cancer cell, the leukemia cell, that has become addicted to that driver no longer has it, it is turned off and that pushes back these leukemia cells, that makes them maybe vulnerable to other therapies. And what is currently going on in clinical trials, because these are very, very new drugs, compounds, that have never been given to human, we are giving them when we have no other therapy left, we do the standard that we know so far works the best upfront, but if the leukemia does come back, and it can happen, then we now offer patients these trials that you mentioned and they can help the patients, which is always the most important thing, and it is tightly controlled that if we realize they hurt the patients, they don’t help, these trials stop. And it’s very regulated and it’s good that way. If we see that in this very difficult setting where the cancer has come back, these new drugs work, then we can now use some earlier in the treatment, and ideally we can use them upfront. Somebody comes in with a diagnosis of leukemia,
we can now use that new targeted therapy maybe with the regular chemo, but we can reduce the regular chemo to have less toxicity and ultimately the goal is to make these leukemia, these cancer cells, go away for good.

Higgins We were talking a little bit about this at the break, but clinical trials really offer us so many opportunities. I treat breast cancer and if it had not been for the hundreds of thousands of women that did the original studies, for example, with lumpectomy and radiation as opposed to mastectomy, we would not be able to treat all of these hundreds of thousands of patients that followed, especially in a very common disease like breast cancer, it affects millions of people eventually. One of the things is, patients enroll in trials and we can benefit people in the future, so hopefully they are doing something good for themselves and benefitting people that will come after them, and I think especially with the targeted therapies, things are moving quickly and these trials, hopefully the advantages will get translated into someone, not only the patient, but someone right down the line who could benefit from that information.

Halene Absolutely. I think it is fair to say that all of our patients hold us to a very high standard because I run a lab, but there is no point to study a disease that does not exist. And so even on the most difficult times when somebody is diagnosed with leukemia, when Somebody is diagnosed with myelodysplasia or with cancer and they have to have some blood taken or a bone marrow biopsy done, we ask them –are you willing to give us some for research, and even in that difficult moment, the patient says yes. And it is the same with clinical trials, patients are willing to enroll because yes, all our data says this hopefully is going to help you, but they are also doing this for the people to come who are going to go through that same difficult situation, and I think that medical scientific community thanks all the patients who enroll.

Higgins We owe so much to the people who are willing to enroll and I think in many of our disease sites like breast cancer especially, it really has revolutionized the way that we do things and I think we are seeing the same with leukemia.

Halene It is, yes.

Higgins There is also a huge part of our cancer center, again, behind the scenes that are a huge part of our cancer center dedicated just to this particular science of running trials and we have the HIC, the IRB and our patients hold us to standards and so does the FDA.

Halene Yes, absolutely.

Higgins We have a whole team behind us that makes sure that we are asking the right questions and that we are monitoring the patients and that we filing all of the side effects so that we can actually move things forward in the most highly regulated process, so I think we are on the forefront, we sit down, I am running a drug trial, we sit down and talk with patients about these trials, but there is a huge team behind us that

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makes everything go well, every single day.

Halene  And the team actually happens at the national level, it happens at an international level. Very frequently, we have a patient who is on a trial or even who is getting an approved drug and suddenly we see something that we don’t understand. We can all pick up the phone, we can all write a quick e-mail to colleagues at other centers in the US and internationally and we all share that information with each other. Again, to keep our patients safe, to make the treatment the best we can and to advance science.

Higgins  And of course, there are the societies that we are all members of; I am a member of ASTRO, you are probably a member of ASH, and these meetings that we go to every year where we can in person share all this information, I really find that to be the highlight of my year going there and being involved in that and presenting our data, it is really a thrill and you feel like, as you said, if you are bridging both sides of that, the research, the trials, then you bring that to your colleagues, so it’s really a great privilege and honor and it’s just a great professional endeavor. Maybe you could talk about some other things that you have done or presented at ASH, any particular research project that you have coming down the pipe that you are excited about?

Halene  We started working based on other studies going on in our lab and our interest in myelodysplasia. We heard this presentation by a Japanese group, Dr. Ogawa’s group, on these recurrent mutations and so-called splicing factors. Splicing factors are those proteins that modify the messenger that takes the information from the nucleus to the protein machinery. And we were very intrigued by one of those proteins and how it could potentially lead to myelodysplasia and then assembled a team from Yale and outside of Yale, from Switzerland to study that protein and that’s called SSF2 and there is a splicing factor and it alters how this protein binds to this RNA, this messenger, and then ends up making abnormal proteins in the cell and reducing the protein level. And what’s been very fascinating is by doing that work, I was able to talk about our work to the members of other foundations, for example, The Evans Foundations. Edward Evans passed away from myelodysplasia and decided to fund research into this and now there is the Evans Foundation and other foundations for other diseases, are now gathering a whole team of researchers interested in that disease and pulling them altogether in a collaborative way to advance this field rapidly. And I think in isolation I couldn’t do that, but now in collaboration with colleagues all over the US, we can advance this field, we can advance our knowledge and we may be able to target what seems to be untargetable, the spliceosome.

Higgins  It’s so fascinating when you have a group that is joining together, physicians, physician scientists, and then hopefully finding people with the vision to support you and this is where we are at a very interesting point in medicine where we need to have a little bit more help as the funding from government and other sources decreases, we need a little more help from philanthropists and other groups to help us, help others.

Halene  Yes, for sure.
Higgins: I think that we are also appreciative of those groups that have that kind of vision and can really join with us to support what are really large groups of physicians, researchers, people in the lab. There is a lot that goes into it and we really need that help. I was wondering what other things in the field, you talked about your research, the spliceosome, I was wondering in terms of the field of hematology, what are some things that people are seeing as the frontier, what would you consider the frontier, where you are heading?

Halene: I think the amazing thing about science today and clinical medicine today is our front is broad. Because we understand the molecular mechanisms and the cells so well, we suddenly understand how different systems that maybe were thought to be completely independent of each other can actually work together, and so we talked about these targeted therapies, those target proteins, kinases and the cytoplasm, now there are new drugs that suddenly can enter the nucleus and then you have to talk about immune therapy. We can modify the immune system of the body to attack these cancer cells, and if you can then take that immune therapy plus these targeted therapies together, we can probably cure cancer.

Dr. Stephanie Halene is Assistant Professor of Medicine and Hematology at Yale School of Medicine. We invite you to share your questions and comments, you can send them to canceranswers@yale.edu or you can leave a voicemail message at 888-234-4YCC, and as an additional resource archived programs are available in both audio and written format at yalecancercenter.org. I am Bruce Barber hoping you will join us again next Sunday evening at 6:00 for another edition of Yale Cancer Center Answers here on WNPR, Connecticut's Public Media Source for news and ideas.